Medical Genetics

Volume II

Clinical Genetics

Part II

Congenital Malformations

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2021

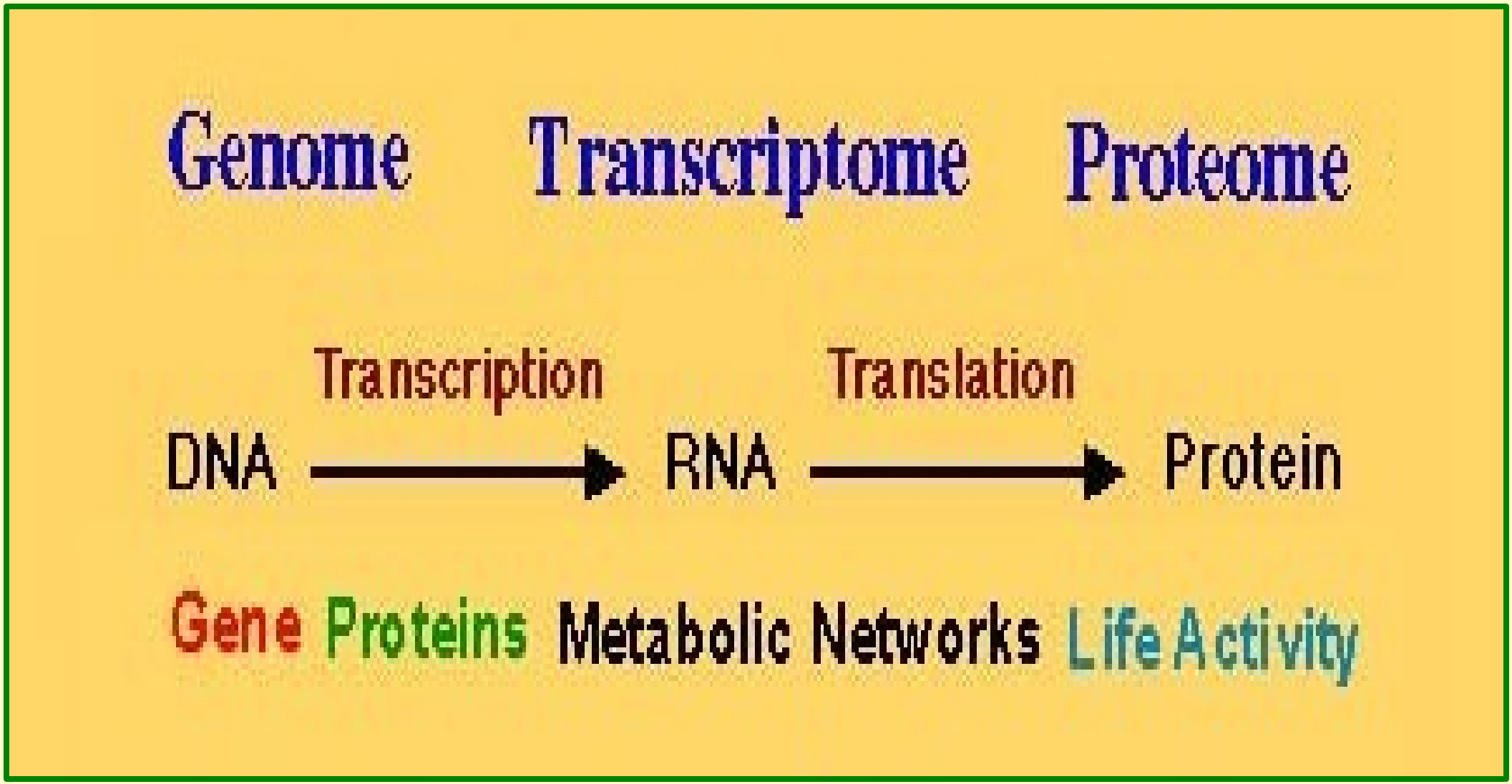
Spectrum of Medical Genetics

Basic Genetics	Clinical Genetics
Part I: Molecular Genetics Part II: Biochemical Genetics Part III: Physiological Genetics Part IIII: Cytogenetics Part V: Pathogenetics Part VI: Pharmacogenetics Part VII: Oncogenetics Part VIII: Immunogenetics Part IX: Formal Genetics Part X: Population genetics Part XI: Developmental Genetics Part XII: Genomics Part XIII: Transcriptomics Part XIV: Proteomics	Part I: Chromosomal Aberrations Part II: Congenital Malformations Part III: Inborn Errors of Metabolism Part IV: Mitochondrial Disorders Part V: Genetic Systemic Syndrome Part VI: Genetic Diseases of The Nervous system Part VII: Genetic Diseases of The Endocrinal system Part VIII: Genetic Diseases of The Cardio-Vascular system Part IX: Genetic Diseases of The Respiratory system Part X: Genetic Diseases of The Gastro-Intestinal system Part XI: Genetic Diseases of The Urinary system Part XII: Genetic Diseases of The Muscular system Part XIII: Genetic Diseases of The Skeletal system Part XIV: Genetic Diseases of The Blood system Part XV: Genetic Diseases of The Immunity system Part XVI: Genetic Diseases of The Male Genital system Part XVII: Genetic Diseases of The Female Genital system Part XVIII: Genetic Diseases of The Ocular system Part XIX: Genetic Diseases of The Auditory system Part XX: Genetic Diseases of The Skin Part XXI: Genetic Psychiatric Disorders
Diagnostic Genetics	**Therapeutic Genetics**
Part I: Molecular Diagnostic Techniques Part II: Cytogenetic Diagnostic Techniques Part III: Biochemical Diagnostic techniques Part IV: Prenatal Diagnosis Part V: Pre-Implantation Diagnosis Part VI: Per-Symptomatic Diagnosis Part VII: Conventional Diagnostic Techniques	Part I: Pharmacologic Therapy Part II: Nutritional Therapy Part III: Replacement Therapy Part IV: Transplantation Therapy Part V: Stem Cell Therapy Part VI: Surgical Intervention Part VII: Genetic Therapy Part VIII: Fetal Therapy Part IX: Conventional Therapy
Prophylactic Genetics	**Applied Genetics**
Part I: Pre-Conception Prophylaxis Part II: Pre-Natal Prophylaxis Part III: Pre-Symptomatic Prophylaxis	Part I: Forensic Genetics Part II: Genetic Counseling Part III: Genetic Screening Part IV: Genetic Engineering Part V: Eugenics

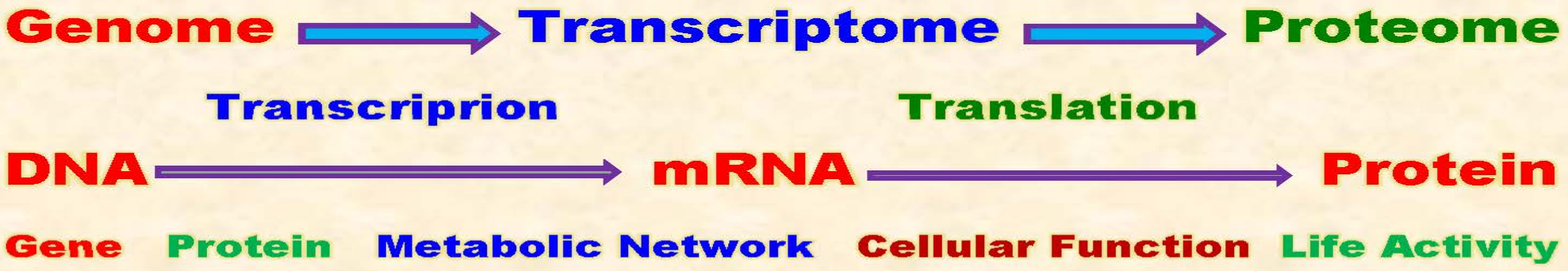
Dogma of Molecular Biology

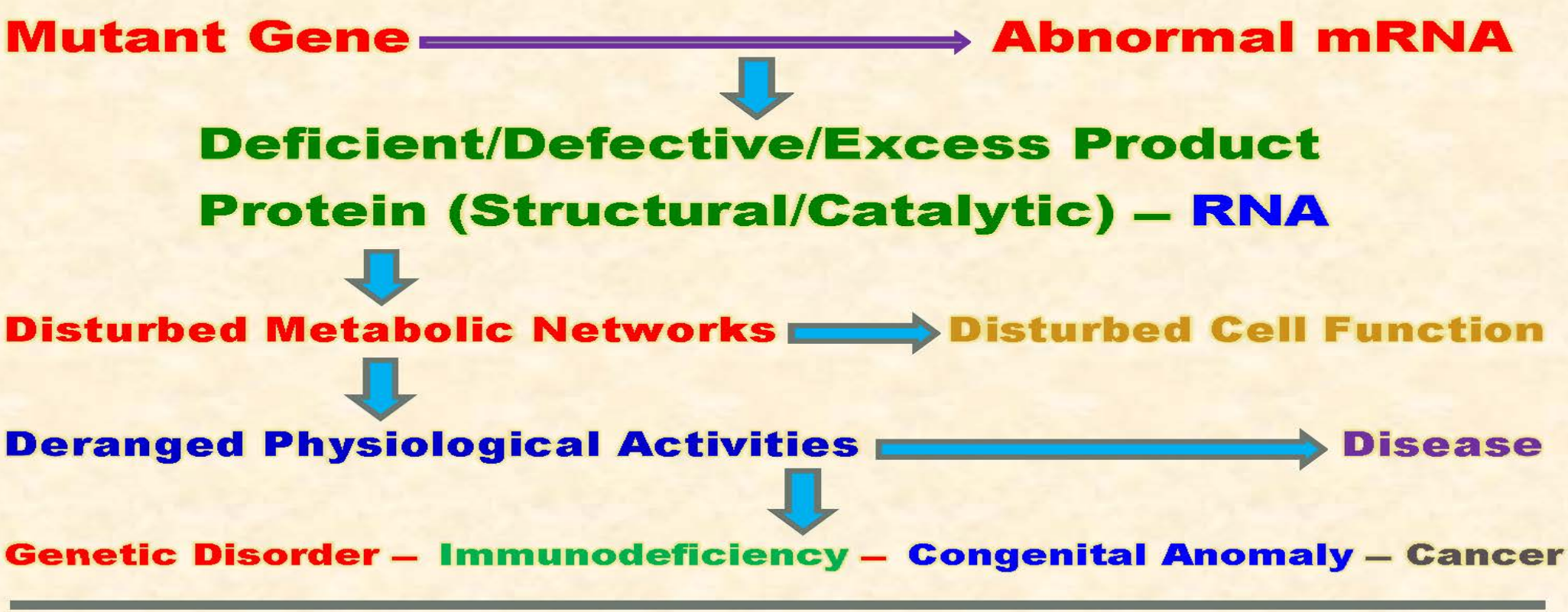
Relation Between The genetic Material and Life Activities

Life Activities at The Molecular level

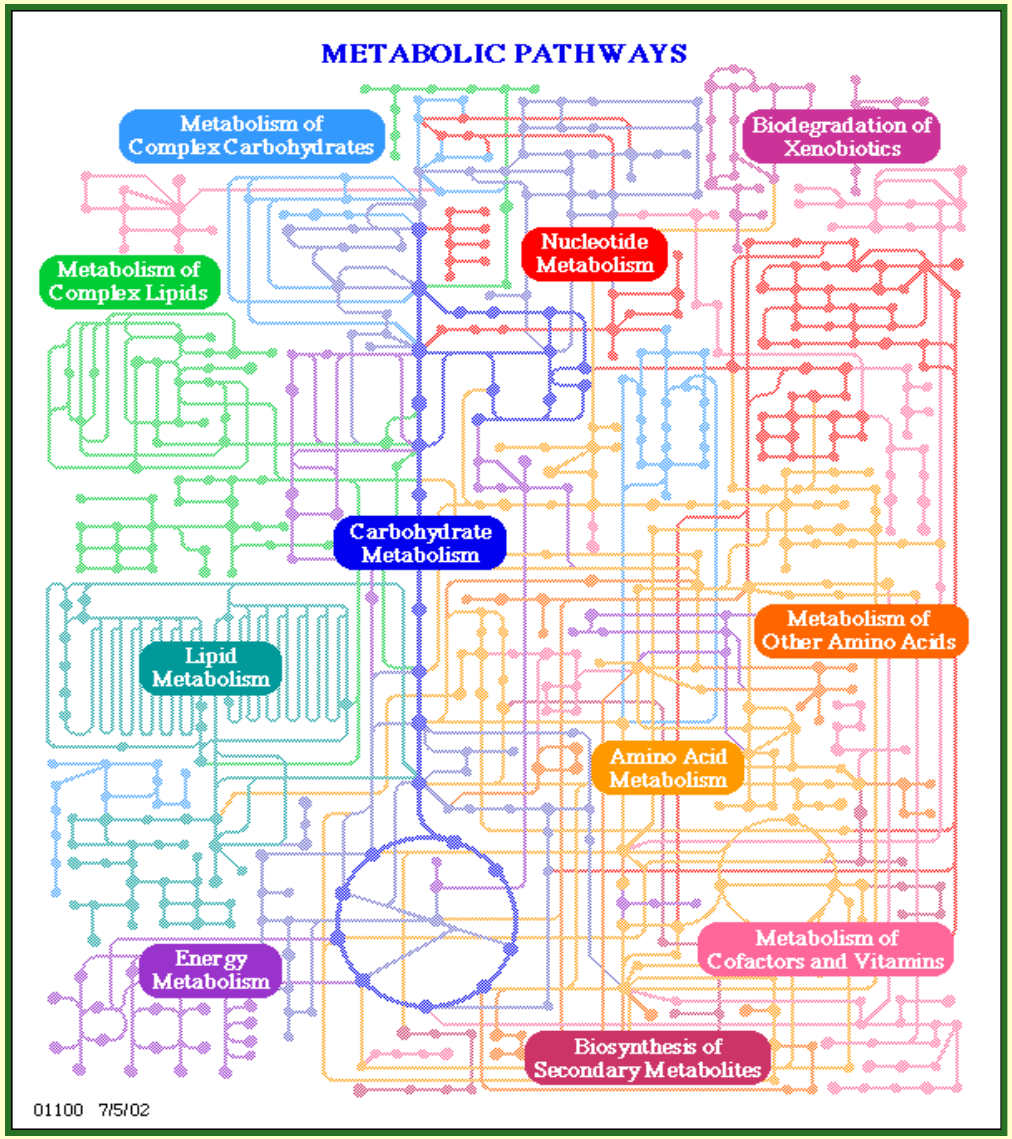


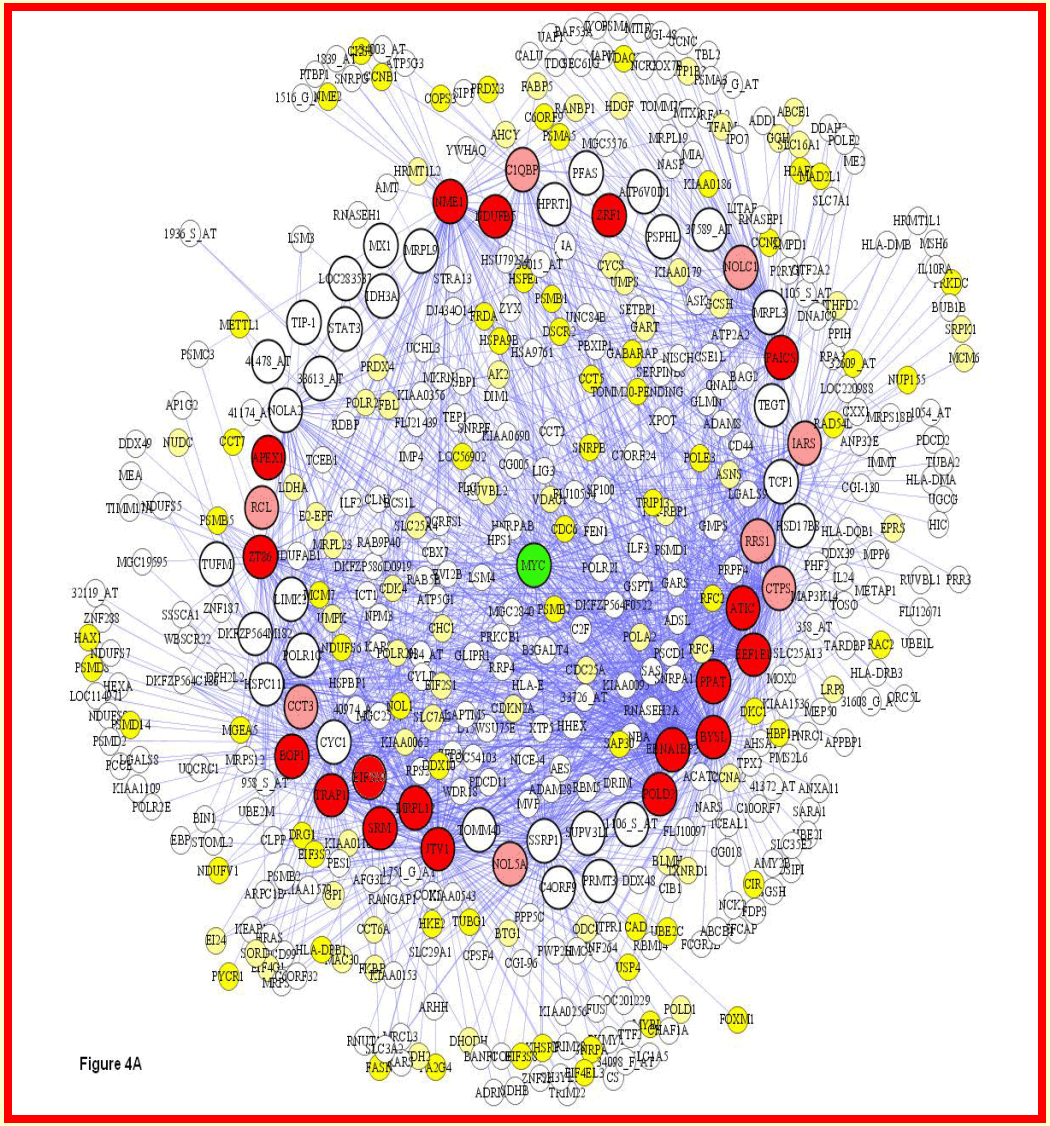
Dogma Of Molecular Pathology In Health And Disease



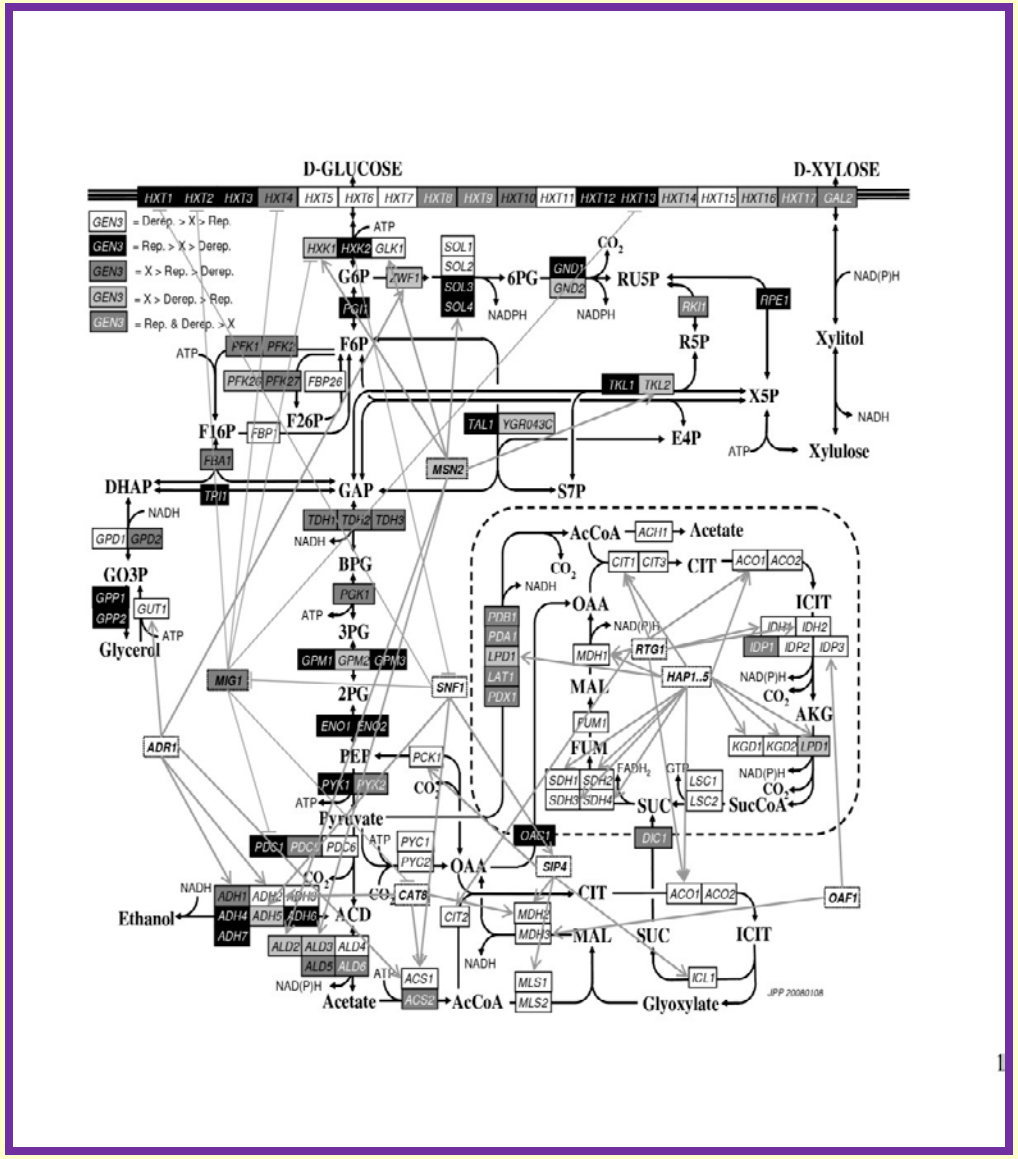


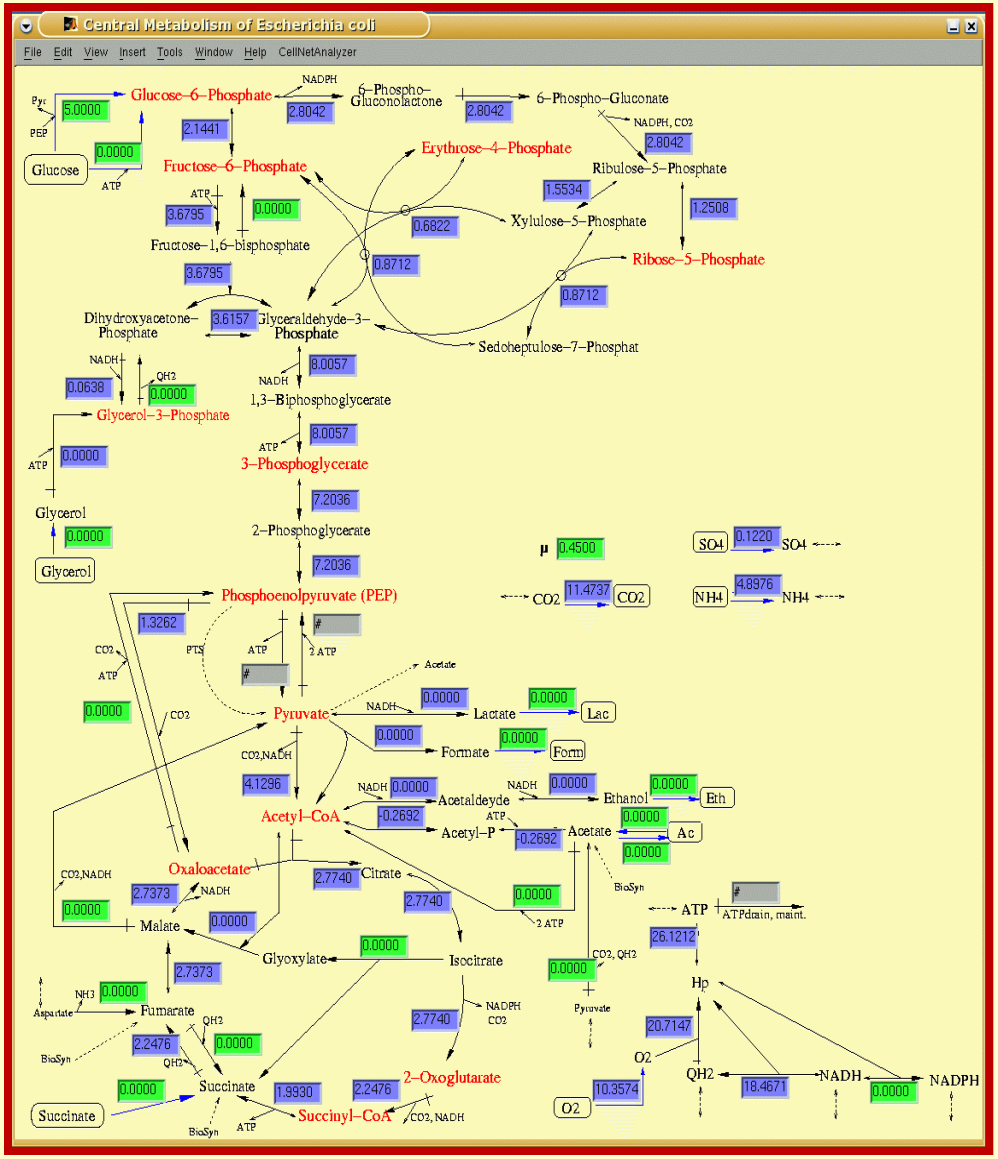
The Concept Of Metabolic Networks



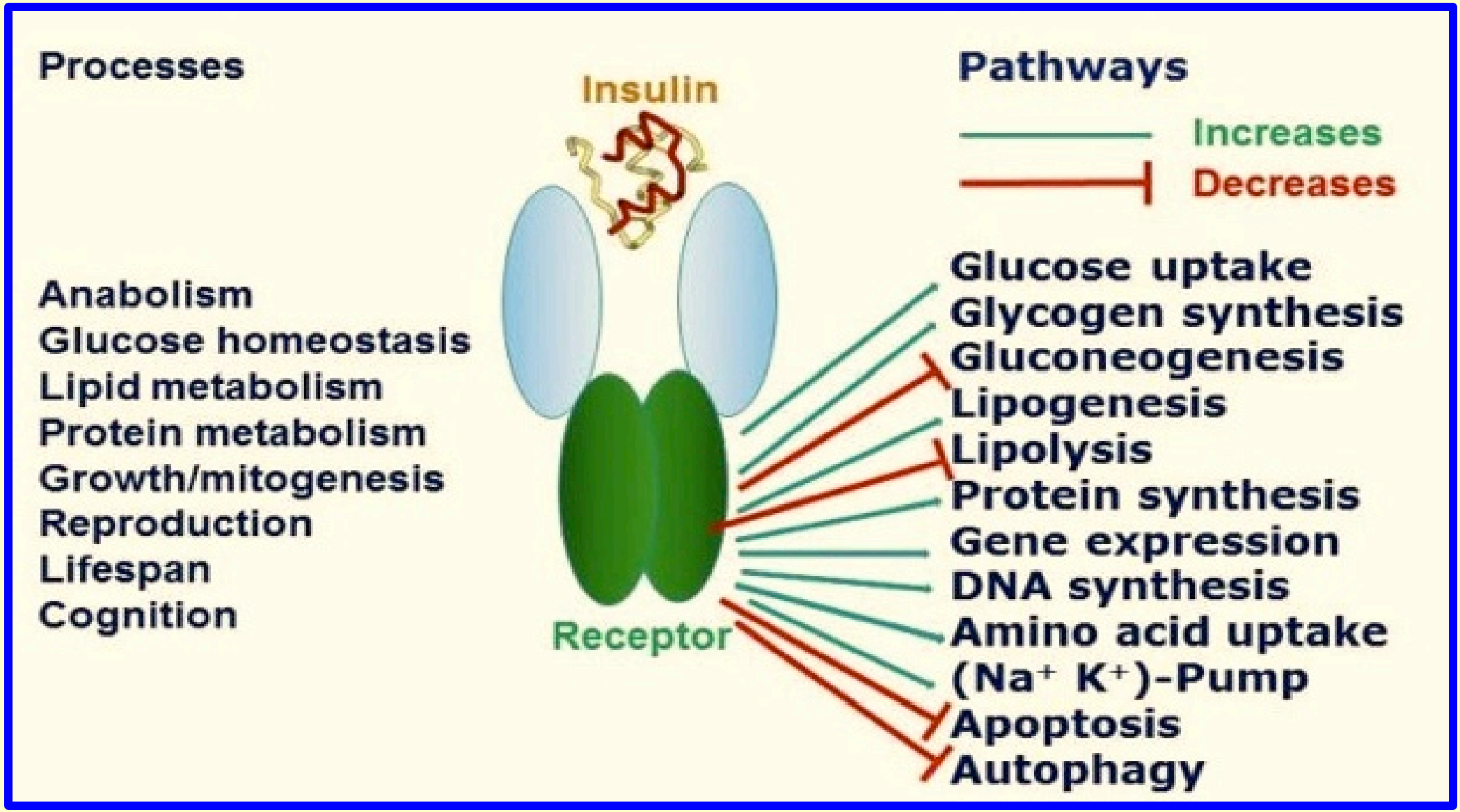


The Concept of Regulatory Networks and Signalling Pathways

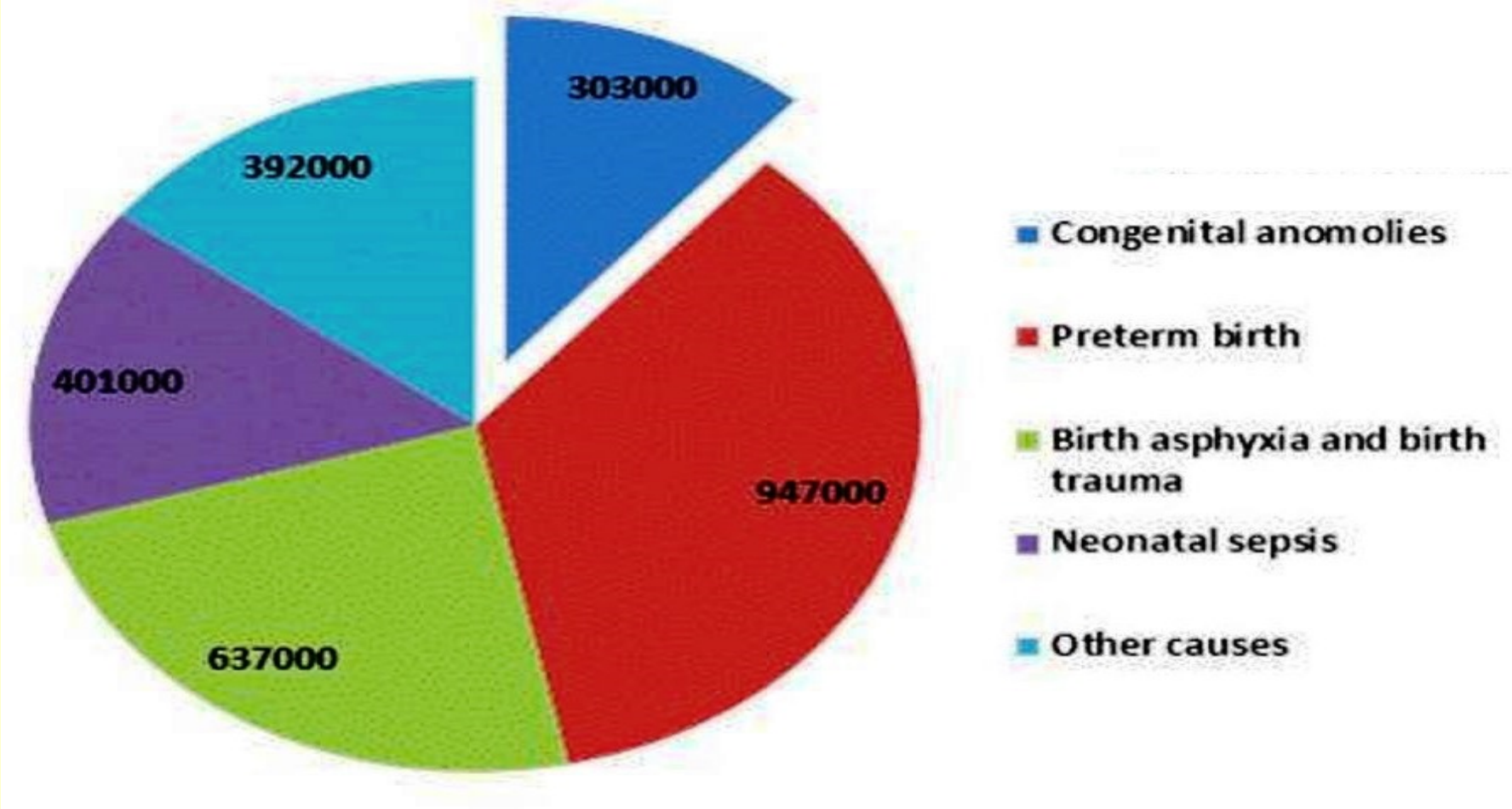




Pleiotropic Actions Of Insulin Through The Insulin Receptor And Insulin Receptor Pathways



Incidence and Impact of Congenital Malformations



Causes of 2.68 million deaths during the neonatal period in 2015, worldwide

Causes of Congenital Malformations & Birth Defects

Cause of malformation	Incidence
1. Multifactorial (genetic causes and environmental causes)	20-30%
2. Single gene disorders	10-20%
3. Chromosomal abnormalities	15%
4. Congenital infections	2.5%
5. Maternal Diabetes mellitus	1.5%
6. Maternal medications & Drugs	1-2%
7. Idiopathic unknown causes	Rest of cases

Congenital anomalies are important causes of infant and childhood deaths, chronic illness and disability. They contribute to long-term disability, which may have significant impacts on individuals, families, health-care systems, and societies.

The Incidence of Major Birth Defects in Infants is 3%. Nearly, an estimated 303 000 newborns die within 4 weeks of birth every year, worldwide, due to congenital anomalies.

The most common congenital anomalies are those affecting the heart, the nervous system, and Down syndrome.

Although congenital anomalies may be the result of one or more genetic, infectious, nutritional or environmental factors, it is often difficult to identify the exact causes of the anomaly in the majority of cases.

A range of normal phenotypic variations, defined as normal spectrum of morphological features with absolutely no medical significance (e.g. epicanthal folds, attached ear lobes), is observed in nearly 4% of the population.

Definition

Congenital malformations, or birth defects, comprise all types of structural abnormalities that develop during intrauterine life, either during embryogenesis and/or fetogenesis, and are existent either as detectable or hidden neonatal structural abnormalities at birth.

Congenital anomalies or congenital disorders comprise, in addition to congenital malformations, underlying functional pathophysiological disorders detectable at birth, including both genetically-determined inborn errors of metabolism detectable at time of birth or later in life, and non-genetic metabolic disorders that temporarily develop during gestation and get completely cured afterwards.

Congenital Anomalies or Congenital Disorders	
1. Congenital Malformations or Birth Defects	**2. Pathophysiological Disorders**
A. Malformations **B. Deformations** **C. Dysplasias** **D. Disruptions.**	**A. Permanent, genetically-determined Inborn Errors of metabolism.** **B. Temporary Metabolic Disorders.**

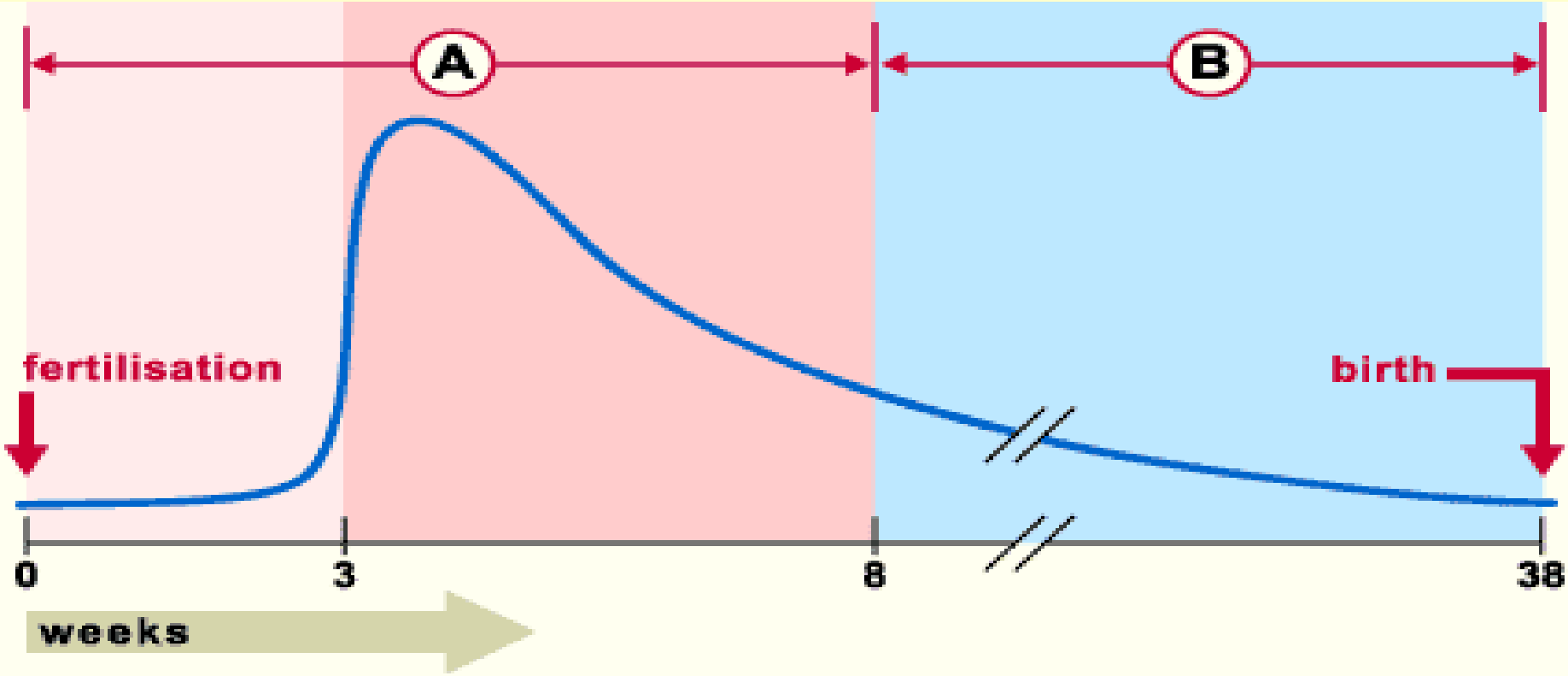
Before the 14th day, a teratogenic injury to the embryo may result in death and spontaneous abortion occurs. Alternatively, due to the extensive whole genome activity of fetal cells, damage to fetal cells and tissues can be repaired and no abnormalities occur.

After that, in the course of the embryonic period, during which numerous mitotic divisions and organogenesis occur, the embryo is very vulnerable and most congenital abnormalities happen during this stage.

Fetopathies occur after the 8th week of gestation and up to delivery. The sensitivity to injurious substances is markedly reduced in the last two trimesters of pregnancy.

Most of the organs already exist and developed by this time and are thus less susceptible to teratogenic effects. One exception is the cerebral cortex which, is especially sensitive to damage between the 8th and 15th weeks of gestation.

The incidence of congenital abnormalities as a function of time



A	Fertilization - 8 weeks post-fertilization : Embryonic period
B	8 weeks post-fertilization – Delivery : Fetal period
0-3 weeks	Death of the embryo is possible
3-8 weeks	Susceptibility to abnormalities is increased
8-38 weeks	Functional disorders of developed organs are more likely

Normal Intrauterine development

Normal intrauterine development, beginning with fertilization and ending with birth of a normal healthy newborn, reflects an extremely complicated dynamic process mediated by the whole genome of the developing embryo/fetus, occuring in an intimate internal environment defined by maternal-related factors, and affected by an external environment that can drastically affect any stage of development.

Actual developmental processes and dynamics are conducted by innumerable numbers of structurally different and functionally distinct regulatory networks and similar numbers of modulating pathways that act in an exquisite and tightly coordinated manner to assure optimal regulation of all processes and proper execution of every step of development.

Genetic regulation of development

Genetic control of development is very complex. It entails the co-ordinated participation of large numbers of master genes that guarantee proper initiation and progression of the different consequent and divergent stages of development according to the genetically-determined predefined profile/design of the developing organism, similar numbers of regulatory genes that control the meticulous harmony between exceedingly large numbers of differentially activated and suppressed structural genes which regulate the synthesis of huge numbers of different categories of RNA molecules, and the exceedingly large numbers of structural, catalytic, and regulatory proteins.

Structural defects and/or functional aberrations in performance or co-operation of any of these genetic regulatory mechanisms underlie the pathogenesis and development of the vast majority of congenital malformations.

Periodic Table of Human Developmental Factors

The human developmental factors listed in the table include ligands and non-receptor, extracellular regulators of the major signaling pathways involved in Developmental Biology. The molecules are presented in a tabular format and color-coded according to family membership or regulatory activity. The information presented was obtained from standard PubMed sources. Due to space constraints, this table does not include all possible modulators of the represented signaling pathways and should not be considered definitive nor comprehensive.

I/II | III | IVa/b | IVc | IVd | IVe | IVf | V | V | V | V | V | VIa | VIb | VIc | VIc | VIc | Vlc | Vld

1* Shh Sonic Hedgehog Patched 1,2	2* Notch-1-4 Neurogenic Locus Notch Homolog Protein DLL1,3,4; Jagged 1, 2; DNER	7* FGF acidic Fibroblast Growth Factor acidic FGF-1; HBGF-1; ECGF FGFR1c,R2b,R3c,R4c					17 Wnt-1 Wingless/Int-1 type Protein 1 Int-1 Frizzled-1,-5,-8; Ryk	18 Wnt-2 Wingless/Int-1 type Protein 2 Frizzled-1,-4,-5,-8	19 Wnt-2b Wingless/Int-1 type Protein 2b Wnt-13 Frizzled-4,-5,-10	20 Wnt-3 Wingless/Int-1 type Protein 3 Frizzled-1,-7,-10; Ryk	21* Wnt-3a Wingless/Int-1 type Protein 3a Frizzled-1,-2,-4,-5,-7,-8,-10+ LRP-6; Ryk; ROR2	22 GDNF Glial cell-derived Neurotrophic Factor Alfl GFRα-1,-2; Ret	8* Activin A Inhibin β_A chain EDF ALK-1,-2,-4; Act RIIA,RIIB; Endoglin; TGF-β RIII	9* Nodal Nodal BMP-16 ALK-2,-4,-7; Act RIIA,RIIB	10 GDF-5 Growth Differentiation Factor 5 BMP-14; CDMP-1 ALK-6; Act RIIA,RIIB; BMPR-II; TGF-β RIII	11* GDF-1 Growth Differentiation Factor 1 Vg1 ALK-4,-7; Act RIIA,RIIB; Act RI; Nodal	12* BMP-4 Bone Morphogenetic Protein 4 BMP-2B ALK-3,-6; BMPR-II; Act RIIA; TGF-β RIII	13* TGF-β2 Transforming Growth Factor beta 2 ALK-1,-2,-5; TGF-β RII,RIII
14* Dhh Desert Hedgehog Patched 1,2	15 Jagged 2 Jagged 2 Notch-1,-2,-3	16 FGF basic Fibroblast Growth Factor basic FGF-2; HBGF-2 FGFR1c,R2c					23* Wnt-5a Wingless/Int-1 type Protein 5a Frizzled-1,-2,-3,-5,-7; Glypican-1; ROR2; Frizzled-4+LRP-5; Ryk	24* Wnt-5b Wingless/Int-1 type Protein 5b ROR2 Unknown Receptor	25 Wnt-6 Wingless/Int-1 type Protein 6 Unknown Receptor	26* Wnt-7a Wingless/Int-1 type Protein 7a Frizzled-5+LRP-6;Frizzled-9,-10	27 Wnt-5b Wingless/Int-1 type Protein 5b Wnt-14b Unknown Receptor	41 Neurturin Neurturin GFRα-2,-1; Ret	23* Activin B Inhibin-β_B chain Act RIIA,RIIB; ALK-2,-4	24* GDF-8 Growth Differentiation Factor 8 Myostatin Act RIIA,RIIB; procGDF-8	25 GDF-6 Growth Differentiation Factor 6 BMP-13; CDMP-2 ALK-1,-2,-3; BMPR-II	26* GDF-3 Growth Differentiation Factor 3 Vgr-2 ALK-4,-7; Act RIIA,RIIB	27 BMP-5 Bone Morphogenetic Protein 5 Unknown Receptor	28* TGF-β3 Transforming Growth Factor beta 3 ALK-1,-2,-5; TGF-β RII,RIII; Endoglin
29* PDGF-A Platelet-derived Growth Factor A PDGF-1 PDGF Rα	30* DLL1 Delta-like 1 Notch-1,-2,-3	31 FGF-3 Fibroblast Growth Factor 3 Int-2 FGF R2b,R2c	32 FGF-4 Fibroblast Growth Factor 4 K-FGF; Hst-1 FGF R1c,R2b,R2c,R3b	33 FGF-8a Fibroblast Growth Factor 8a AIGF FGF R2c	34 FGF-9 Fibroblast Growth Factor 9 GAF FGF R1c,R2c	35* FGF-19 Fibroblast Growth Factor 19 FGF-15 (mouse) FGF R1c or R4+Klotho β	36 Wnt-4 Wingless/Int-1 type Protein 4 Frizzled-6	37 Wnt-5a Wingless/Int-1 type Protein 5a Frizzled-1-2-3-5-7; Glypican-1; ROR2; Frizzled-4+LRP-5; Ryk	38 Wnt-5b Wingless/Int-1 type Protein 5b ROR2 Unknown Receptor	39 Wnt-6 Wingless/Int-1 type Protein 6 Unknown Receptor	40 Wnt-7a Wingless/Int-1 type Protein 7a Frizzled-5+LRP-6;Frizzled-9,-10	41 Neurturin Neurturin GFRα-2,-1; Ret	42* Activin C Inhibin-β_C chain Act RIIA,RIIB	43 GDF-11 Growth Differentiation Factor 11 BMP-11; CDMP-3 Act RIIA,RIIB; ALK-4,-5,-7	44 GDF-7 Growth Differentiation Factor 7 BMP-12; CDMP-1 ALK-3,-6; BMPR-II; Act RIIA	45* BMP-15 Bone Morphogenetic Protein 15 Vgr-1 ALK-6; BMPR-II; Act RIIA	46 BMP-6 Bone Morphogenetic Protein 6 Vgr-1 ALK-2,-3,-6; Act RIIA,RIIB; BMPR-II	47* MIS Müllerian Inhibiting Substance AMH ALK-2,-3,-5,-6; MIS RII
48* PDGF-B Platelet-derived Growth Factor B PDGF-2 PDGF Rα,Rβ	49* DLL3 Delta-like 3 Notch-1	50 FGF-7 Fibroblast Growth Factor 7 KGF FGF R2b	51 FGF-5 Fibroblast Growth Factor 5 HBGF-5 FGF R2c	52 FGF-17 Fibroblast Growth Factor 17 FGF R2c	53 FGF-16 Fibroblast Growth Factor 16 FGF R2c	54 FGF-21 Fibroblast Growth Factor 21 FGF R1c or R4+Klotho β	55 Wnt-7b Wingless/Int-1 type Protein 7b Frizzled-1,-10	56 Wnt-8a Wingless/Int-1 type Protein 8a Frizzled-1,-8,-10	57 Wnt-8b Wingless/Int-1 type Protein 8b Unknown Receptor	58 Wnt-9a Wingless/Int-1 type Protein 9a Wnt-14 Unknown Receptor	59 Wnt-9b Wingless/Int-1 type Protein 9b Wnt-15; Wnt-14b Unknown Receptor	60 Artemin Artemin Enovin; Neublastin GFRα-1,-3; Ret	61 Activin E Inhibin-β_E chain Act RIIA,RIIB	62 BMP-3 Bone Morphogenetic Protein-3 Osteogenin; BMP-3A ALK-4; Act RIIB	63 BMP-9 Bone Morphogenetic Protein 9 GDF-2 Act RIIA,RIIB; ALK-1,-2; BMPR-II; Endoglin	64 GDF-9 Growth Differentiation Factor 9 ALK-5; BMPR-II	65 BMP-7 Bone Morphogenetic Protein 7 Op-1 Act RIIA,RIIB; BMPR-II; ALK-1,-6	66 Lefty-A Lefty-A Lefty-2; Ebaf Cripto; Nodal
67* PDGF-C Platelet-derived Growth Factor C SCDGF PDGF Rα	68 DLL4 Delta-like 4 Notch-1,-4	69 FGF-10 Fibroblast Growth Factor 10 KGF-2 FGF R2b	70 FGF-6 Fibroblast Growth Factor 6 HBGF-6; Hst-2 FGF R1b,R2b,R2c	71 FGF-18 Fibroblast Growth Factor 18 FGF R2c,R4	72 FGF-20 Fibroblast Growth Factor 20 FGF R1c,R3b,R3c,R4	73* FGF-23 Fibroblast Growth Factor 23 Phosphatonin FGF R1c,R3c,R4+Klotho	74* Wnt-10a Wingless/Int-1 type Protein 10a Unknown Receptor	75* Wnt-10b Wingless/Int-1 type Protein 10b Wnt-12 Frizzled-5	76 Wnt-11 Wingless/Int-1 type Protein 11 Frizzled-5, -7; Ryk	77* Wnt-16b Wingless/Int-1 type Protein 16b Unknown Receptor	78* Norrin Norrie Disease Protein NDP Frizzled-4	79 Persephin Persephin PSP GFRα-4; Ret	80* Inhibin α Inhibin α TGF-β RII; Act RIIA	81 BMP-3b Bone Morphogenetic Protein-3b GDF-10; BIP Unknown Receptor	82 BMP-10 Bone Morphogenetic Protein 10 Act RIIA,RIIB; BMPR-II; ALK-1, 3, 4	83* GDF-15 Growth Differentiation Factor 15 MIC-1;PLAB Unknown Receptor	84* BMP-8 Bone Morphogenetic Protein 8 Op-2; BMP-8b Unknown Receptor	85* Lefty-B Lefty-B Lefty-1; BMP-10 Cripto; Nodal
86* PDGF-D Platelet-derived Growth Factor D SCDGF-B PDGF Rβ	87* DNER Delta and Notch-like EGF-related Receptor BET Notch-1	88 FGF-22 Fibroblast Growth Factor 22 FGF R2b																

FAMILY KEY

- **I:** Hedgehog Family
- **II:** PDGF Family
- **III:** Notch/DSL Family
- **IV:** FGF Family, with subfamilies (a-f)‡
- **V:** Wnt Family
- **VI:** TGF-β Family, with subfamilies (a-d)‡: GDNF, Activin, TGF-β, BMP/GDF

‡ Subfamilies grouped according to amino acid identity, with a few exceptions that are listed according to function.

STRUCTURE KEY

Monomer; Homodimer; Heterodimer; Single Pass Transmembrane; GPI Linked; Soluble

See Notes section below for additional information

Note Number — Structure

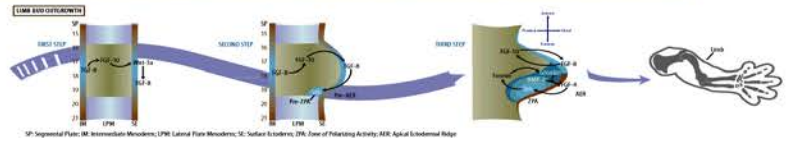
8* 13-15 / 100 — Observed Mature Molecular Weight (kDa) / % Amino Acid Identity between mouse & human

Activin A — Abbreviated Full Name

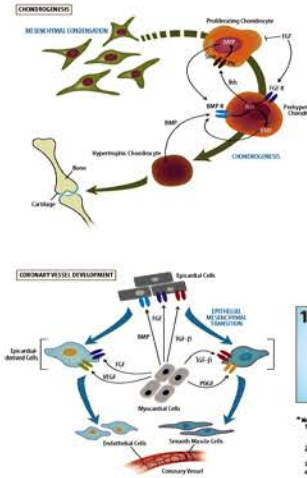
Inhibin β_A chain — Complete Name

EDF — Alternate Name

ALK-1,-2,-4; Act RIIA,RIIB; Endoglin; TGF-β RIII — Receptors (or in the case of Regulators, Ligands)



SP: Segmental Plate; IM: Intermediate Mesoderm; LPM: Lateral Plate Mesoderm; SE: Surface Ectoderm; ZPA: Zone of Polarizing Activity; AER: Apical Ectodermal Ridge



REGULATORS

89* Gas1 Growth Arrest Specific Shh; Shh	90 HIP Hedgehog Interacting Protein HHIP Shh; Dhh, Ihh	91* MAGP-1 Microfibril-associated Glycoprotein 1 MAGP-1A; MFAP-2 Notch-1; Jagged 1,2; DLL1	92* MAGP-2 Microfibril-associated Glycoprotein 2 MAP-5; MP25 Notch-1; Jagged 1	93* FGF-BP FGF Binding Protein Hbp17 FGF-1,-2,-7, -10, -22	94* Klotho KL; Klotho-α FGF R1c,R3c,R4	95* Klotho β KLB FGF R1c,R2c,R3c,R4	96* Follistatin FSH-suppressing Protein FS Activin A; GDF-8, -11; BMP-4, -5, -6, -7	97 FLRG Follistatin-related Gene Protein FSTL3; FSRP Activin A; GDF-8	98* Cripto CR-1; TDGF-1; CFC-2 GDF -1, -3; Nodal; TGF-β1; Activin B; TMEFF-1; ALK-4	99 Cryptic Cryptic CR-1 GDF-1; Nodal	100* TMEFF1 Tomoregulin-1 Cbin92 Cripto-1	101* GASP-1 GDF-associated Serum Protein-1 WFIKKNRP; WFIKKN2 GDF-8,-11	102* GASP-2 GDF-associated Serum Protein 2 WFIKKN; WFIKKN1 GDF-8, -11					
103 Noggin Noggin BMP-2, -4, -5, -6, -7; GDF-5, -6	104* Chordin Chd BMP-2, -4, -7; TSG	105 Chordin-like 1 Chordin-like 1 CRD(L1; Neuralin; Veerostatin BMP-4, -4/7	106 Chordin-like 2 Chordin-like 2 CRD(L2; BNF-1 BMP-2, -4, -6, -7; Activin A; TSG	107* CRIM1 Cysteine-rich Motor Neuron 1 Precursor CRIM BMP-4, -7; TGF-β2; Nodal; PDGF-B	108* CRIM2 Cysteine-rich Motor Neuron 2 Precursor KCP; Kielin BMP-2; TGF-β1; Activin A	109* CV-2 Crosswinkless-2 CR(M3; BMP(3) BMP-2, -4, -5, -6	110 Brorin Brain-specific Chordin-like Protein VWC-2 BMP-2, -4	111* TSG Twisted Gastrulation BMP-2, -4; Chordin; TGF-β	112 DAN Differential Screening Gene Aberrant in Neuroblastoma DAND1; NBL1 BMP-2, -4, -7; GDF-5	113 Gremlin Gremlin Drm; DAND2 BMP-2, -4, -7; GDF-5	114 PRDC Protein Related to Dan & Cerberus Gremlin-2; DAND3 BMP-2, -4	115 Cerberus Cerberus DAND4, Cer1 Nodal; BMP-4	116* COCO COCO Dante; Gremlin-3; Cer2, DAND5 Nodal; BMP-4	117* SOST SOST Sclerostin BMP-2, -4, -6; LRP-5, -6	118* USAG Uterine Sensitization-associated Gene 1 WISE; SOSTDC-1; Ectodin BMP-2, -4, -6; 7; LRP-6			
119* CTGF Connective Tissue Growth Factor CCN2; IGFBP-8 LRP-6; BMP-4; TGF-β1	120* Cyr61 Cysteine-rich, Angiogenic Inducer 61 CCN1; GIG1 TGF-β	121* NOV Nephroblastoma Overexpressed Gene CCN3; IGBP-3 Notch-1; BMP-3	122* LTBP-1 Latent TGF-β Binding Protein 1 TGF-β Binding Protein 1 LAP; ECM	123* LTBP-2 Latent TGF-β Binding Protein 2 procGF-β; ECM	124* LTBP-3 Latent TGF-β Binding Protein 3 procGF-β; LAP; ECM	125* LTBP-4 Latent TGF-β Binding Protein 4 LAP; ECM	126 Vasorin Vasorin SLIT-like 2 TGF-β1,2,3	127* Decorin Bone Proteoglycan II PG-S2; PG40 TGF-β1; BMP-4	128* Biglycan Bone/Cartilage Proteoglycan I SLRR1A; PG-S1 TGF-β1; BMP-4	129 Asporin Asporin PLAP1 BMP-2; TGF-β1	130* TSK Tsukushi ARK54; C2-induced gene 4 BMP-4; -7; Chordin; DLL1; Nodal; FGF-8	131* SPARC Secreted Protein, Acidic, Cysteine-rich Osteonectin; EM40 PDGF-AA, PDGF-BB; TGF-β1, FGF-2	132* SPP24 Secreted Phosphoprotein 24 Secreted Phosphoprotein 2 BMP-2	133* Dermatopontin Dermatopontin TIMMP; ED-1 Decorin; TGF-β1; BMP-2	134* CTHRC1 Collagen triple Helix Repeat-containing Protein 1 NARC1 Frizzled-1, -3, -6; ROR2; Wnt-3a, -5a, -11			
135 Dkk-1 Dickkopf-1 LRP-5, -6; Kremen-1, -2	136* Dkk-2 Dickkopf-2 LRP-5, -6; Kremen-1, -2	137* Dkk-3 Dickkopf-3 REIC LRP-5, -6; Kremen-1, -2	138 Dkk-4 Dickkopf-4 LRP-5, -6; Kremen-1, -2	139 sFRP-1 Secreted Frizzled Related Protein 1 SARP2; FrzA Wnt-1, -2, -3a, -5a, Frizzled-6, -8, -7	140 sFRP-2 Secreted Frizzled Related Protein 2 SARP1 Wnt -1, -3a, -4, -5a	141 sFRP-3 Secreted Frizzled Related Protein 3 FrzB Wnt-1, -3a, -8	142* sFRP-4 Secreted Frizzled Related Protein 4 FrpHE; FrzB2 Frizzled-1; Wnt-2a, -8	143* sFRP-5 Secreted Frizzled Related Protein 5 SARP3; FRP1B Wnt-5a, -11	144* WIF-1 Wnt Inhibitory Factor 1 Wnt -1, -4, -8; Frizzled-8	145* R-Spondin 1 Roof Plate-specific Spondin 1 Rspo1 Wnt -1; LRP-6; Frizzled-5, -8; Heparin 1, -2	146 R-Spondin 2 Roof Plate-specific Spondin 2 Rspo2, Cristin-2 Wnt -1; LRP-6; Frizzled-8	147* R-Spondin 3 Roof Plate-specific Spondin 3 Rspo3; Cristin-1 Wnt -1; LRP-6; Frizzled-8	148* R-Spondin 4 Roof Plate-specific Spondin 4 Rspo4; Cristin-4 Unknown Receptor	149* Myocilin Myocilin TIGR Frizzled-1, -2, -10; sFRP-1, -3; WIF-1	150* Kremen-1 Kringle-coding Gene Marking Eye & Nose 1 Krm-1 Dkk-1, -2; LRP-5, -6	151 Kremen-2 Kringle-coding Gene Marking Eye & Nose 2 Krm-2 Dkk-1, -2, -4		

Notes

1. Contains both palmitic acid and cholesterol; Multiversization is reported to occur due to hydrophobic interactions between cholesterol and palmitate adduct
2. Type I transmembrane homeodomain proteins of intracellular and extracellular fragments
3. Forms heterodimers with BMP-5, -6, and -7
4. Forms a heterodimer with TGF-β2; LAP dimer and TGF-β dimer are noncovalently associated
5. Contains both palmitic acid and cholesterol; Multiversization is reported to occur due to hydrophobic interactions between cholesterol and palmitate adduct
6. Proteolytically processed in a Notch-like fashion to generate trans-tyrosyl activation; Both inhibits and potentiates Notch-1 activity
7. Forms a dimer when complexed with heparan sulfate
8. Forms a disulfide-linked heterodimer with inhibin α chain (inhibin A) or inhibin β_A chain (Activin AB)
9. Forms a heterodimer with GDF-1
10. Forms a heterodimer with Nodal
11. Forms heterotrimers with BMP-5, -6, and -7, and a noncovalent heterodimer with GDF-1
13. Forms heterodimers with TGF-β1 and -β3; LAP dimer and TGF-β dimer are noncovalently associated
14. Contains both palmitic acid and cholesterol; Only two sources for DERS (Sertoli and Schwann cells; Multiversization is reported to occur due to hydrophobic interactions between cholesterol and palmitate adducts
21. Glycosylation and palmitoylation are necessary for secretion and activity
23. Forms a homodimer with Inhibin-β_A chain (Activin BC); Inhibin-α chain (Inhibin B) or Inhibin-β_B chain (Activin AB)
24. GDF-8 propeptide binds Act RIB and mature GDF-8, blocking its activity
25. Only binds Notch in cis; will not activate Notch
26. Forms a disulfide-linked homodimer and a disulfide-linked heterodimer with PDGF-A
27. The unprocessed mature form is biologically active
28. Forms a disulfide-linked homodimer and a disulfide-linked heterodimer with PDGF-B
29. Forms a homodimer with Inhibin-β_A chain (Activin AC), Inhibin-α chain (Inhibin A) or Inhibin-β_B chain (Activin AB)
30. Recent assays at Lx1 (Lx1 identity does not include 17 aa insert in the kinase protein)
31. Cannot form disulfide bonds; Forms a noncovalent heterodimer with GDF-6; Active BMP-15 is phosphorylated; Dephosphorylated BMP-15 is inactive
32. The unprocessed mature form is biologically active
33. Forms a disulfide-linked homodimer and a disulfide-linked heterodimer with PDGF-A
34. Forms a disulfide-linked heterodimer with β-subunits
35. Regulates bile acid synthesis and release; Amino acid sequence: identical to that found in between human FGF-19 and mouse FGF-15
42. Antagonizes Activin A, possibly by forming Activin AC heterodimers
44. Recent assays at Lx1 (Lx1 identity does not include 17 aa insert in the kinase protein)
45. Cannot form disulfide bonds; Forms a noncovalent heterodimer with GDF-9; Active BMP-15 is phosphorylated; Dephosphorylated BMP-15 is inactive
47. The unprocessed mature form is biologically active
48. Forms a disulfide-linked homodimer and a disulfide-linked heterodimer with PDGF-B
49. Only binds Notch in cis; will not activate Notch
50. Molecular weight listed is the predicted value
51. Molecular weight listed is the predicted value
52. Molecular weight listed is the predicted value
53. Molecular weight listed is the predicted value
54. Antagonizes Activin A, possibly by forming Activin BE heterodimers
62. Acts as a BMP antagonist
64. Cannot form disulfide bonds; Forms a noncovalent homodimer with BMP-15; Active GDF-9 is phosphorylated; Dephosphorylated GDF-9 is inactive
65. BMP-7 preurgement and mature form associate similar to LAP/TGF-β1; Forms heterodimers with BMP-2, -4, and GDF-7
66. 42 kDa preprotein is bioactive; 34 kDa form is inactive; 28 kDa form is active
67. PDGF-C is activated intracellularly
73. Promotes phosphate excretion
74. Molecular weight listed is the predicted value
75. Blocks preadipocyte differentiation
77. Biomarker for congenital heart defects
78. Regulates angiogenesis in the eye and eye via the Wnt signaling pathway; Disulfide-linked homodimers oligomerize to form higher order structures
80. Forms a disulfide-linked heterodimer with β1 subunits
81. A divergent member of the TGF-β superfamily
84. BMP-4A and -4B are duplicate genes with 96% amino acid precursor identity; Molecular weight listed is the predicted value
85. 42 kDa preprotein is bioactive; 34 kDa form is inactive; 28 kDa form is active
86. PDGF-D is activated extracellularly
87. Neuronal protein restricted to soma or dendrites
89. Gas1 requires COO for HH binding; Concentrates Shh on the cell surface
91. MAGP-1 induces Notch-1 ECD release; May form a multimer with ECM proteins
92. MAGP-2 induces both Notch-1 and Jagged-1 ECD release; May form a multimer with ECM proteins
93. Association of FGF-BP with HSPGs weakens HSPG attachment of FGFs and promotes their release; FGF-BP enhances the mitogenic effects of FGF-1
94. Alternative transcript produces a secreted form. Belongs to the glycosyl hydrolase 1 family
95. Fundamental regulator of aging and calcium/phosphorus metabolism
96. FS-315 is the serum scavenger for Activins
98. Binds to Activin RIB/ALK-4 or to Nodal/ALK-4 to generate low efficacy signaling receptors
100. Regulates Nodal but not Activin signaling
101. Possesses trypsin inhibitory activity; Binds both the mature and procogerent of GDF-8
102. Possesses trypsin inhibitory activity; Binds both the mature and procogerent of GDF-8
104. Isoforms are tissue-specific and display unique BMP-binding affinities
107. Binds to BMP preprocursors intracellularly and inhibits BMP activity; Soluble form is 70-75 kDa
108. Enhances BMP signaling
109. Both enhances and inhibits BMP signaling; CV-2 is proteolytically cleaved to generate an N- and a C-terminal fragment that form a disulfide-linked heterodimer
111. Enhances BMP binding to Chordin, thus promotes proteolysis of Chordin (to promote BMP activity)
116. Antagonizes Nodal and BMP
117. Antagonizes Wnt and BMP activity; Mutations cause bone dysplasias
118. Antagonizes Wnt (by binding LRP) and BMP activity
119. Binds Fibronectin
120. Antagonizes BMP activity; Promotes TGF-β1 activity
121. Intracellular form is 413 kDa; Secreted form is 70 kDa
123. Secreted, cytoplasmic, and nuclear
124. Secretion is dependent upon covalent association with LAP; LTBP-1 has the strongest association with the ECM
125. Incorporated into the ECM
127. Secreted proteoglycan (SLRP); Antagonizes or potentiates TGF-β signaling
128. Antagonizes BMP activity; Forms a complex with BMP and Chordin; Percent amino acid identity listed is between rat & human
131. ECM protein; Blocks/antagonizes VEGF and PDGF signaling
132. Highly phosphorylated ECM protein
133. ECM protein; Forms a complex with Decorin and TGF-β, increasing TGF-β activity
134. Inhibits TGF-β signaling and enhances the interaction of Wnt/ROR2 complexes
136. Antagonizes Wnt signaling when bound to Kremen-2; Without Kremen-2, activates LRP-6 and Wnt signaling
137. Acts extracellularly to promote Wnt-mediated signaling
142. Acts as a circulating phosphocin (promotes phosphate excretion) with FGF-23
143. Molecular weight listed is the predicted value
144. The WIF domain interacts with palmitic acid adduct on Wnts
145. Potentiates Wnt signaling; Blocks LRP-6 internalization by binding Kremen
147. Potentiates Wnt signaling; Signals independently through LRP-6
148. Molecular weight listed is the predicted value
149. Activates the Wnt pathway
150. At high levels of LRP-5/6, Kremen-1 collaborates with Dkk-1 to antagonize Wnt signaling. In the absence of Dkk-1, Kremen-1 maximizes LRP-6 on the cell surface

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Signal Transduction Pathways During Development

Cell–cell interactions via signal-transduction pathways are crucial in the coordination of embryonic development. Typically, signaling pathways are activated by the binding of a specific ligand to a trans-membrane receptor which in turn leads to the modification of cytoplasmic transducers. Subsequently, these transducers activate transcription factors that ultimately alter gene expression resulting in differential transcription of activated genes.

One of the most surprising findings about signaling processes is that only a few pathways are involved in, and are responsible for, most of embryonic development. These comprise seven major pathways: the wingless related (Wnt), Transforming Growth Factor-β (TGF-β), Hedgehog (Hh), Receptor Tyrosine Kinase (RTK), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), Notch and nuclear receptor pathways.

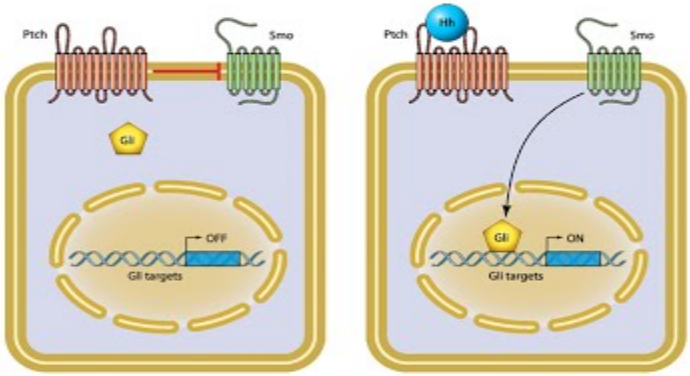
Important Signalling Transduction Pathways/Networks

1. Wnt Signaling Pathways/Networks	**12. Nitric Oxide Signaling Pathway/Networks**
2. Hedgehog Signaling Pathway/Networks	13. Ttransforming Growth Factor Beta (TGFB) Pathway/Networks
3. The Notch Signaling Pathway/Networks	14. mTOR (Mammalian Target of Rapamycin) Pathway/Networks
4. Insulin Signaling Pathways/Networks	15. Cytokine and NF-κB Signaling Pathway/Networks
5. Redox Signaling Pathways/Networks	16. STING-Dependent Signaling Pathway/Networks
6. Lipid Signaling Pathways/Networks	17. PI 3-Kinase/Akt Signaling Pathway/Networks
7. Retinoic Acid Signaling Pathway/Networks	18. Epinephrine Signal Transduction Pathway/Networks
8. Estrogen Signaling Pathway/Networks	19. cAMP-Dependent Signaling Pathway/Networks
9. The MAPK/ERK Pathway/Networks	20. The JAK-STAT signaling pathway/Networks
10. Calcium Signaling Pathways/Networks	21. Apoptosis Signaling Pathways/Networks Extrinsic Caspases Signaling Pathways/Networks Intrinsic Caspases Signaling Pathways/Networks Initiator/Executive Caspases Signaling Pathways/Networks TNF Signaling Pathways/Networks Fas Death Receptor Signaling Pathways/Networks
11. Hippo Signaling Pathway	22. Oncogenic Signaling Pathways/Networks The PI3K-Akt and Ras-ERK Pathways/Networks VEGF Mediated Signaling Pathway/Networks FAK-Src Signaling Pathway/Networks Androgen Receptor (AR) Signaling/Networks The Hippo-YAP Signaling Pathway/Networks

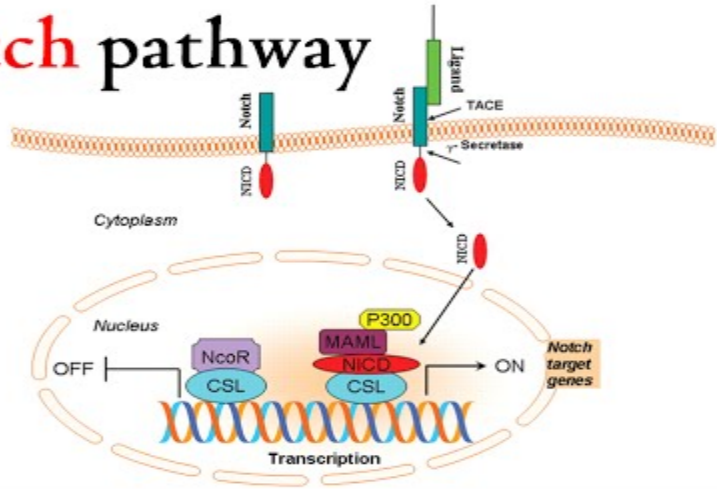
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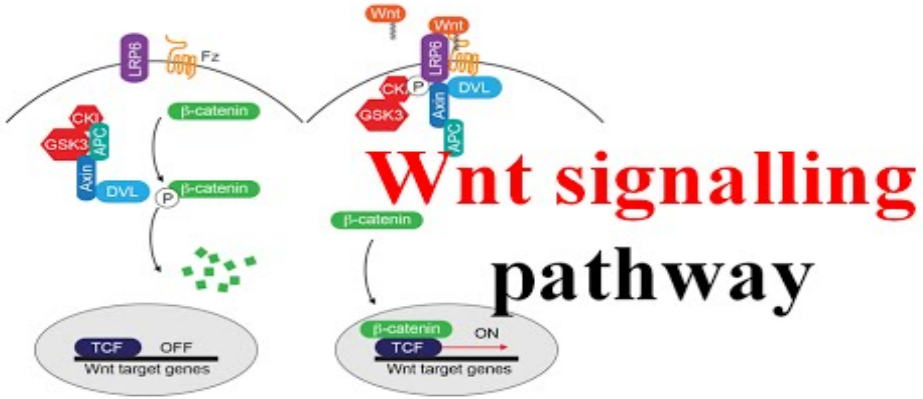
Hedgehog pathway



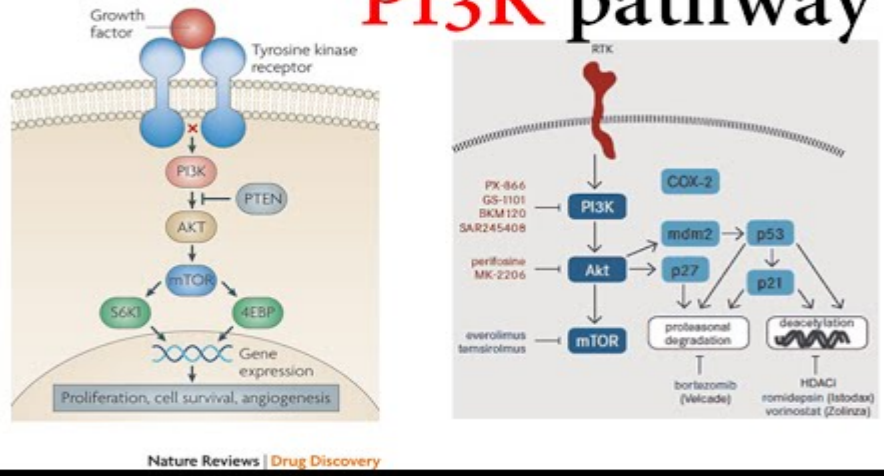
Notch pathway



Wnt signalling pathway

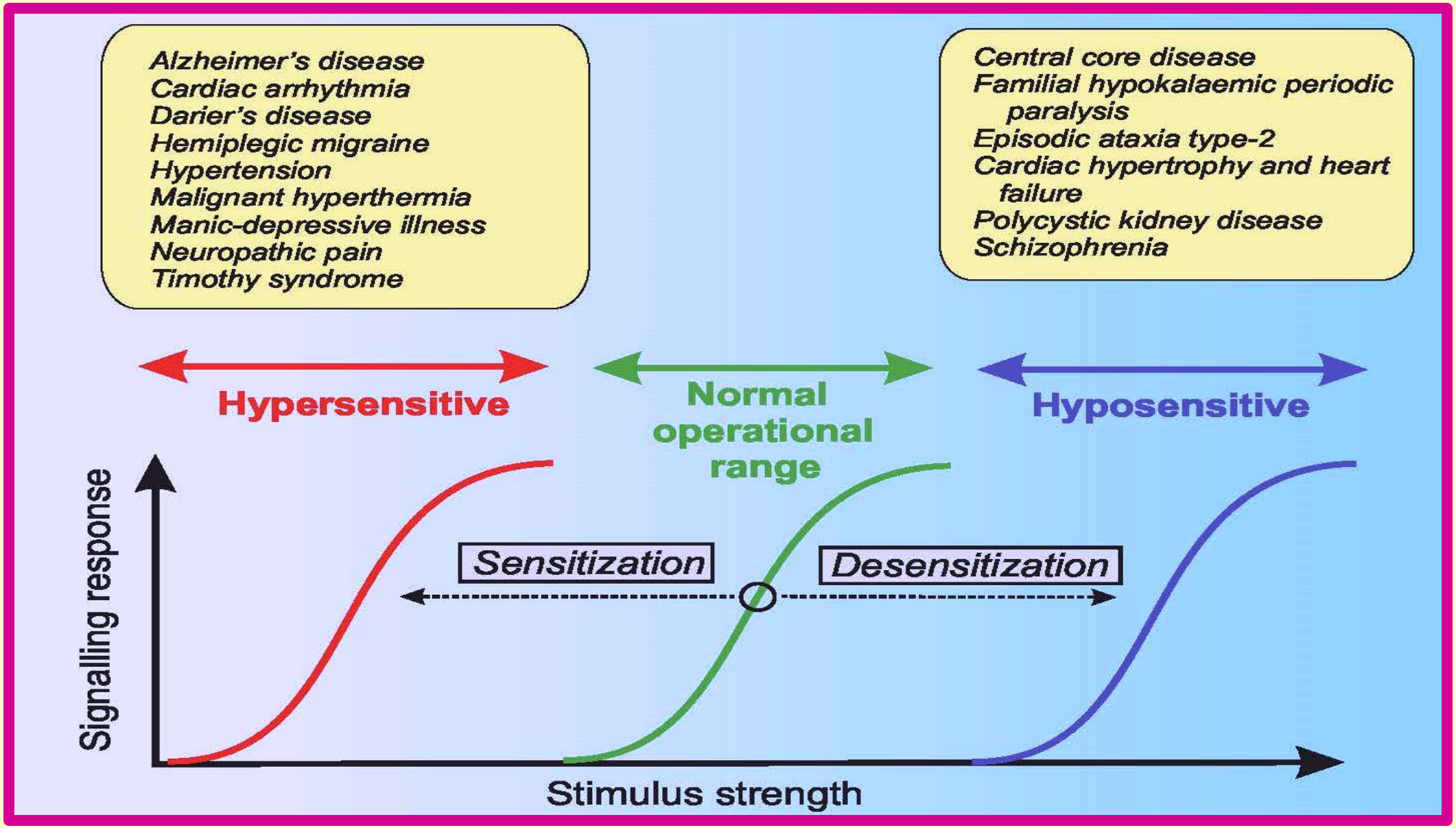


PI3K pathway



Nature Reviews | Drug Discovery

Regulatory Functions Of Signal Transduction Pathways In Normal/Abnormal Development



Developmental Signalling Pathways

1. The Wnt signaling pathways are a group of signal transduction pathways composed of proteins that pass signals from outside of a cell through cell surface receptors to the inside of the cell.

Three distinct Wnt signaling pathways have been characterized: the canonical Wnt pathway, the non-canonical planar cell polarity pathway, and the non-canonical Wnt/calcium pathway. All three Wnt signaling pathways are activated by the binding of a Wnt-protein ligand to a receptor on the cell surface (Frizzled family receptor) which passes the biological signal to a receptor protein (Dishevelled protein) inside the cell.

The canonical Wnt pathway is mainly involved in regulation of transcription of genes and the non-canonical planar cell polarity pathway regulates the architecture of the cell cytoskeleton that is responsible for the shape of the cell while the non-canonical Wnt-

Wnt signal transduction pathways are highly conserved since they have similar structures and functions across many species from fruit flies to humans.

Wnt signalling was first identified for its role in carcinogenesis, but has since been recognized for its critical regulatory functions in embryonic development. The embryonic processes it controls include body axis patterning, cell fate specification, cell proliferation, and cell migration. These processes are necessary for proper formation of important tissues including bone, heart, and muscle.

The clinical importance of this pathway has been demonstrated by mutations that lead to a variety of diseases, including breast and prostate cancer, glioblastoma, type II diabetes, and many others.

2. The hedgehog signaling pathway constitutes a critical signaling regulatory pathway during development of all known animals. In the embryo, it regulates morphogenesis of a variety of tissues and organs. Hedgehog proteins are essential regulators of a variety of critical developmental processes including growth, patterning and morphogenesis. In adults, they control proliferation of stem cells.

There are three human hedgehog (HH) proteins: Sonic hedgehog, Desert hedgehog and indian hedgehog. Each of them is encoded by a different gene and expressed at different times of development in specific cell types. They are tightly controlled by highly complex, yet divergent, transcriptional enhancers and suppressor species of miRNAs. The release, diffusion and binding of these proteins to the transmembrane domain proteins is controlled by various other proteins including Skinny hedgehog (Sit), Dispatched (Disp), Tout-velu (Ttv) and Hedgehog-interacting protein (Hip).

Aberrant activation of the HH pathway has been linked to multiple types of human cancer particularly basal cell carcinoma. Disruption of HH signaling during embryonic development, either through genetic mutations or maternal teratogen consumption, leads to a wide spectrum of severe developmental disorders such as holoprosencephaly.

A. Sonic Hedgehog Protein (SHH)

This signal transducing protein plays key roles in regulating vertebrate organogenesis, such as growth of digits on limbs and organization of the brain. Sonic hedgehog protein is encoded by SHH gene located on long arm of chromosome 7, is a critical morphogen, i.e. a molecule that diffuses to form a concentration gradient and has different effects on the cells of the developing embryo depending on its concentration. Mutations of the SHH gene are the leading causes of holoprosencephaly and other midline cerebral defects. SHH remains important in the adult since it controls cell division of adult stem cells and has been implicated in development of some cancers.

B. Desert Hedgehog Protein (DHH)

This regulatory signal transducing protein is encoded by the DHH gene located on the long arm of chromosome 12. Defects in this protein have been associated with partial gonadal dysgenesis (PGD) accompanied by mini-fascicular polyneuropathy. This protein may be involved in both male gonadal differentiation and peri-neurial development.

C. Indian Hedgehog Protein (IHH)

This protein is encoded by the IHH gene located on the long arm of chromosome 2. It specifically plays a major regulatory role in bone growth and differentiation and is involved in regulating the differentiation, proliferation and maturation of chondrocyte especially during stage of endochondral ossification. Its effects are regulated by feedback control of a parathyroid hormone-related peptide (PTHrP). Known mutations in this gene are linked to many developmental bone malformations including brachydactyly type A1 and acro-capito-femoral dysplasia.

3. The Notch signaling pathway

The notch signaling pathway is a highly conserved cell signaling system present in most multicellular organisms. Notch is present in all metazoans, and mammals possess four different notch receptors, referred to as NOTCH1, NOTCH2, NOTCH3, and NOTCH4. The notch receptor is a single-pass trans-membrane receptor protein..

This signalling pathway is important for cell-cell communication, which involves gene regulation mechanisms that control multiple cell differentiation processes during embryonic and adult life. Notch signaling also has a role in the following processes:

1. **Neuronal function and development.**
2. **Stabilization of arterial endothelial and angiogenesis.**
3. **Regulation of many processes of myocardial formation, crucial cell communication events between endocardium and myocardium during the formation of the valve primordial and ventricular development and differentiation and cardiac valve homeostasis.**

4. Timely cell lineage specification of both endocrine and exocrine pancreas.
5. Binary fate decisions of gut cells to drive cell differentiation along either the secretory or the absorptive functional lineage.
6. Expansion of the hematopoietic stem cell compartment during bone development and commitment to the osteoblastic lineage.
7. Expansion of the hemogenic endothelial cells along with signaling axis involving Hedgehog signaling pathway.
8. T cell lineage commitment from common lymphoid precursor.
9. Regulation of cell-fate decision in mammary glands at several distinct development stages.
10. Control of the actin cytoskeleton through the tyrosine kinase.
11. Notch signaling is required in the regulation of polarity and mutation experiments have shown that loss of Notch signaling causes abnormal anterior-posterior polarity in somites.
12. Notch signaling plays an important regulatory role during body left-right asymmetry determination in vertebrates.

Notch signalling pathway has been found to be dys-regulated in many cancers, and faulty notch signaling is implicated in many diseases including T-cell acute lymphoblastic leukemia, Tetralogy of Fallot, Multiple Sclerosis, Alagile syndrome, Cerebral Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy, and many other disease states.

Notch signaling in adult brain function

In addition to its multiple developmental functions, Notch pathway proteins and ligands are persistently expressed in cells of the adult nervous system, suggesting a role in CNS plasticity throughout life. Experimentally induced animal mutations results in deficits in spatial learning and memory. Dys-regulation of Notch proteins in post-natal life due to mutations of the genes encoding Notch proteins probably underlies the neurodegenerative manifestations of many neurological and cognitive disorders including Alzheimer disease and pre-senile dementias.

4. The fibroblast growth factor signaling pathway

The fibroblast growth factors (FGFs) represent one of the relatively few families of extracellular signaling peptides that have pivotal key regulatory role in metazoan development. FGFs are required for multiple processes in both protostome and deuterostome groups. Given the wide range of regulatory roles attributed to the FGFs, it is perhaps not surprising that misregulation of this signalling pathway has been implicated in a number of human disease conditions.

Although the birth of normal, as well as of malformed, neonate is the most common outstanding consequence throughout human life on the earth since thousands of years, too little is known about the basic framework of real regulatory mechanisms that underlie normal development, and much lesser is known about aberrant pathogenetic-pathophysiological processes that ultimately lead to abnormal intrauterine embryonic/fetal development.

Congenital Malformations/Disorders Associated With Defects Of Some Signal Transduction Pathways

Signal Transduction Pathway	Associated Congenital Malformation-Disorders
Sonic Hedgehog Protein	Holoprosencephaly, Midline Cerebral Defects
Desert Hedgehog Protein	Partial Gonadal Dysgenesis (PGD) accompanied by Mini-Fascicular Polyneuropathy
Indian Hedgehog Protein	Developmental bone malformations including Brachydactyly Type A1, Acro-Capito-Femoral Dysplasia.
Notch Signalling Pathway	Cancer, T-cell Acute Lymphoblastic Leukemia, Tetralogy of Fallot, Multiple Sclerosis, Alagile syndrome, Cerebral Arteriopathy with Sub-cortical Infarcts, Leukoencephalopathy, Alzheimer disease, Pre-senile dementias.
Wnt Signaling Pathway	Breast and Prostate Cancer, Glioblastoma, Type II diabetes

Stages of Normal development

A. Fertilization

This stage comprises immediate and consequent early post-fertilization genomic alterations. It accomplishes two separate biological activities: sex determination of the developing fetus and start of development.

B. Early embryonic development

This stage comprises many consecutive stages: cell cleavage or cell division, hyperplasia or cell multiplication, temporal imprinting of non-relevant genes, cell differentiation, cell specialization, cell localization, cell migration, and apoptosis.

C. Morphogenesis

This stage involves final shaping of specialized cells and tissues, it involves histogenesis, and organogenesis, patterning, positioning in accordance with the predefined, species-specific and genetically-determined programmed pattern and design of all anatomical parts and landmarks of the developing embryo, or embryogenesis.

Differentiation

This process implies structural and functional differentiation of cells of the embryo to form the specialized structures and functions that they will have in the adult. They form neurons, blood cells, skin cells, muscle cells, etc. These cells are organized into tissues, the tissues into organs, the organs into systems that ultimately constitute the fetus.

Differentiation is mediated primarily by still unclear widespread genetic activation-imprinting mechanisms where genes needed for functions of the specialized differentiated cell remain in an active state, where as genes whose functions are not needed any more for the differentiated cell are imprinted or suppressed and remain inactive within the genome of the cell.

Patterning

During this phase of embryogenesis, cells produced by cleavage organize themselves in layers and masses, a process called gastrulation, and the pattern of the main configuration of the future organism appears as:

1. Cephalic-Caudal axis pattern.
2. Ventral-Dorsal axis pattern.
3. Right side-Left side axis pattern.
4. Proximal and distal axis pattern.

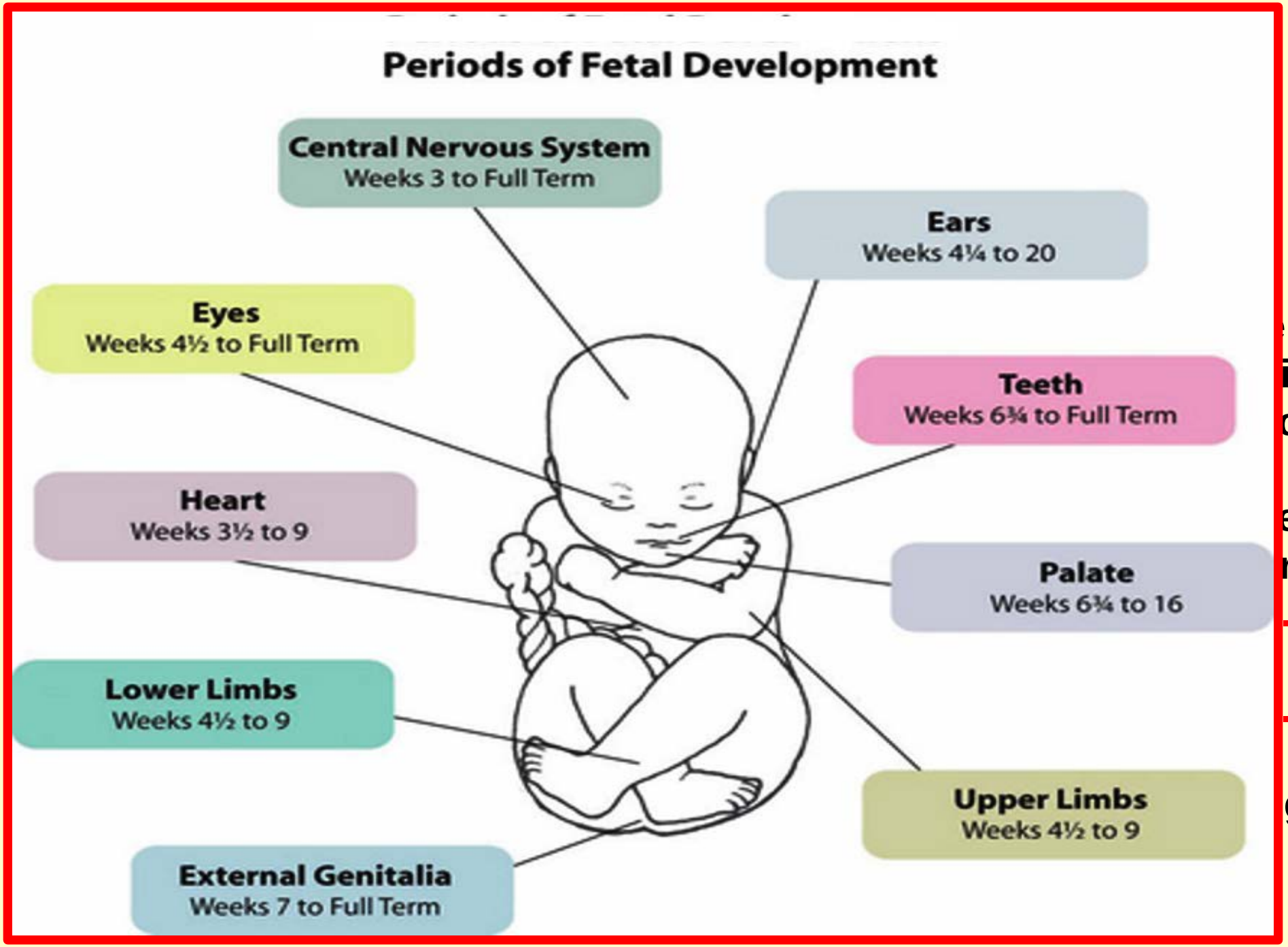
Gastrulation signifies full expressive capacity of the cells and results in formation of the three major germ layers: the ectoderm, the mesoderm and the endoderm.

Growth

After all the body systems of the developing organism are formed, most species go through a period of growth. Growth occurs by the formation of new cells and synthesis of more extracellular matrix. It is an ever continuing biological process that begins with fertilization and remains as an active life process till death.

Apoptosis

Like growth, apoptosis or programmed cell death represents an ever continuing biological phenomenon that begins during early embryonic development and remains as an active life process till death. Apoptosis is an essential developmental process necessary for normal embryogenesis and fetal maturation. Brain development and organization involves apoptosis of many regions at different stages of development. Shaping of fingers and final outcome of vistigial organs are other examples of developmental roles played by apoptosis during normal development.

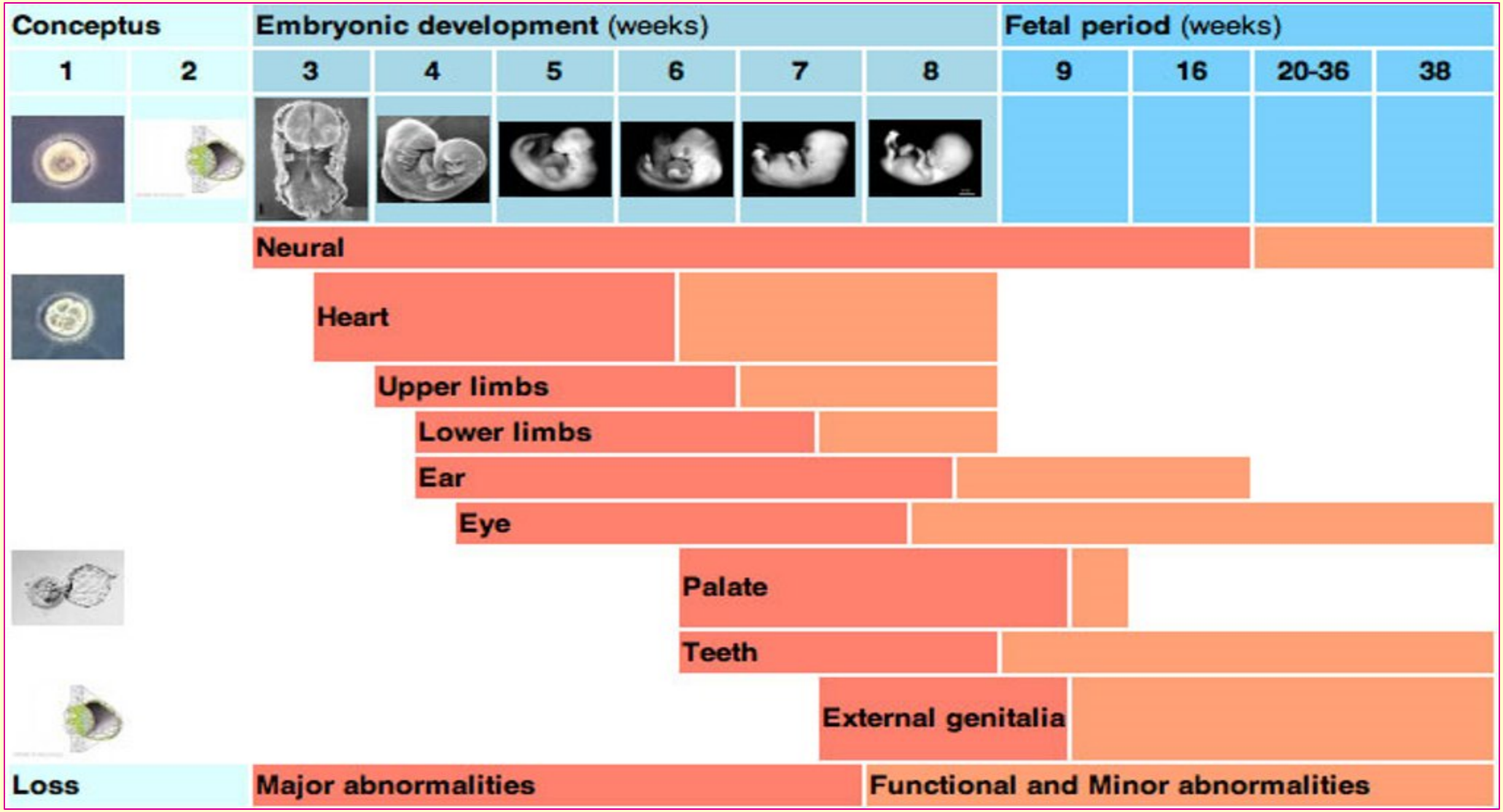


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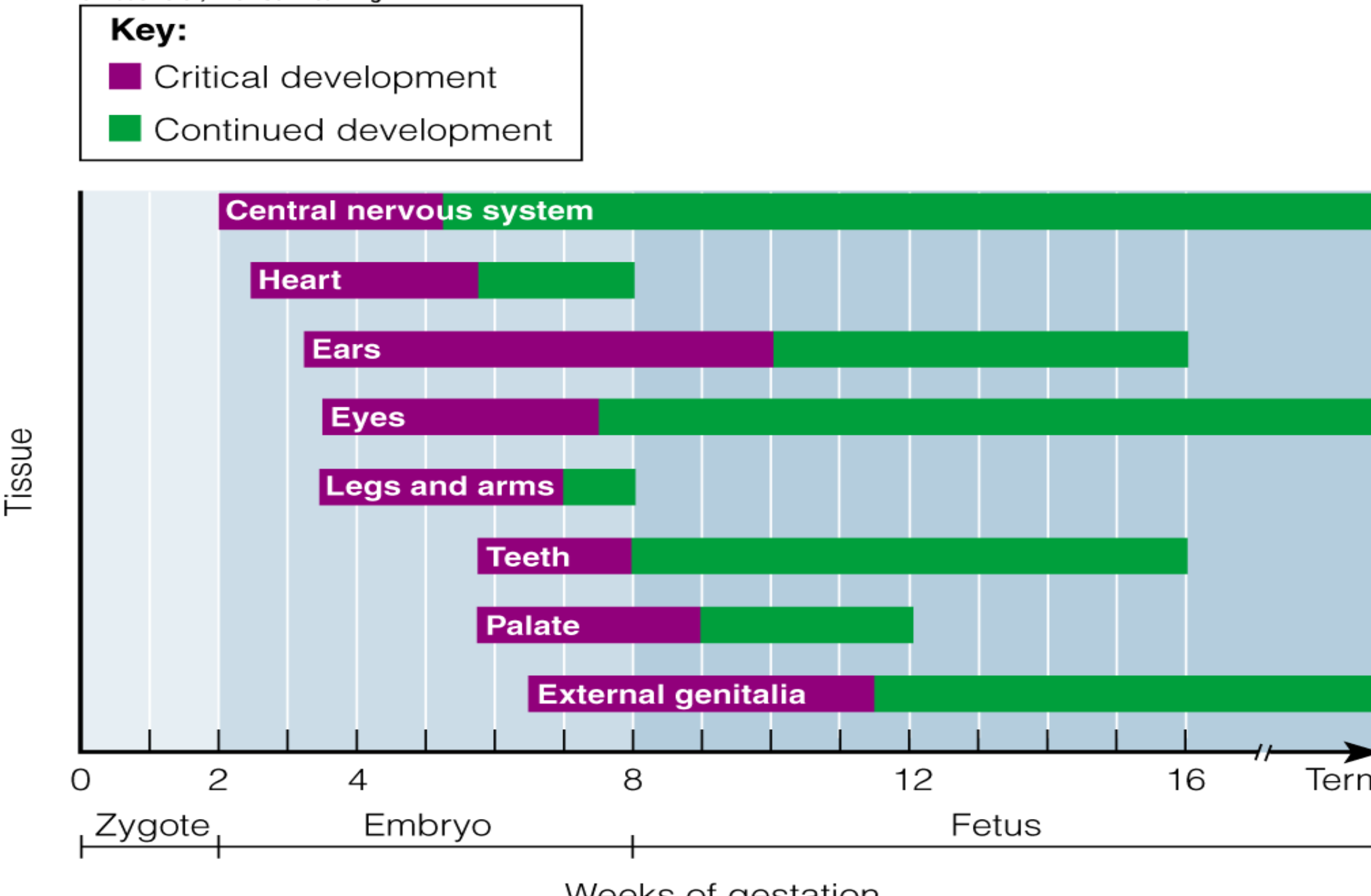
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Critical Periods of Human Development



Hill, M.A. (2018, March 29) Embryology Human-critical periods of development

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Teratology

Teratology is the study of all aspects related to, and involved in, teratogenesis or the development and pathogenesis of congenital structural malformations during embryonic and fetal life.

Teratogenesis comprises the study of different types and nature of teratogens, or causes and factors that cause and predispose to pathogenesis of malformations, nature and mediation of genetic, pathogenetic mechanisms, and non-genetic, pathophysiological alterations, teratogenic mechanisms underlying the development of congenital malformations, factors that affect and modify the susceptibility to actions and effects of teratogens, different types of teratogenic malformations, prenatal diagnostic investigations of congenital malformations, available therapeutic approaches to some malformations, and preventive aspects of teratogenesis.

Teratogenesis

Teratogenesis refers to intrauterine pathogenetic mechanisms and pathological processes that can adversely affect the normal developmental stages of the embryo and/or the fetus and result in causation of congenital malformations. Teratogenesis can be classifies into two major subtypes: spontaneous teratogenesis and induced teratogenesis.

A. Spontaneous teratogenesis refers to development of congenital malformations without a history of maternal-embryonic-fetal exposure during prenatal-antenatal periods to any of the known teratogenic factors.

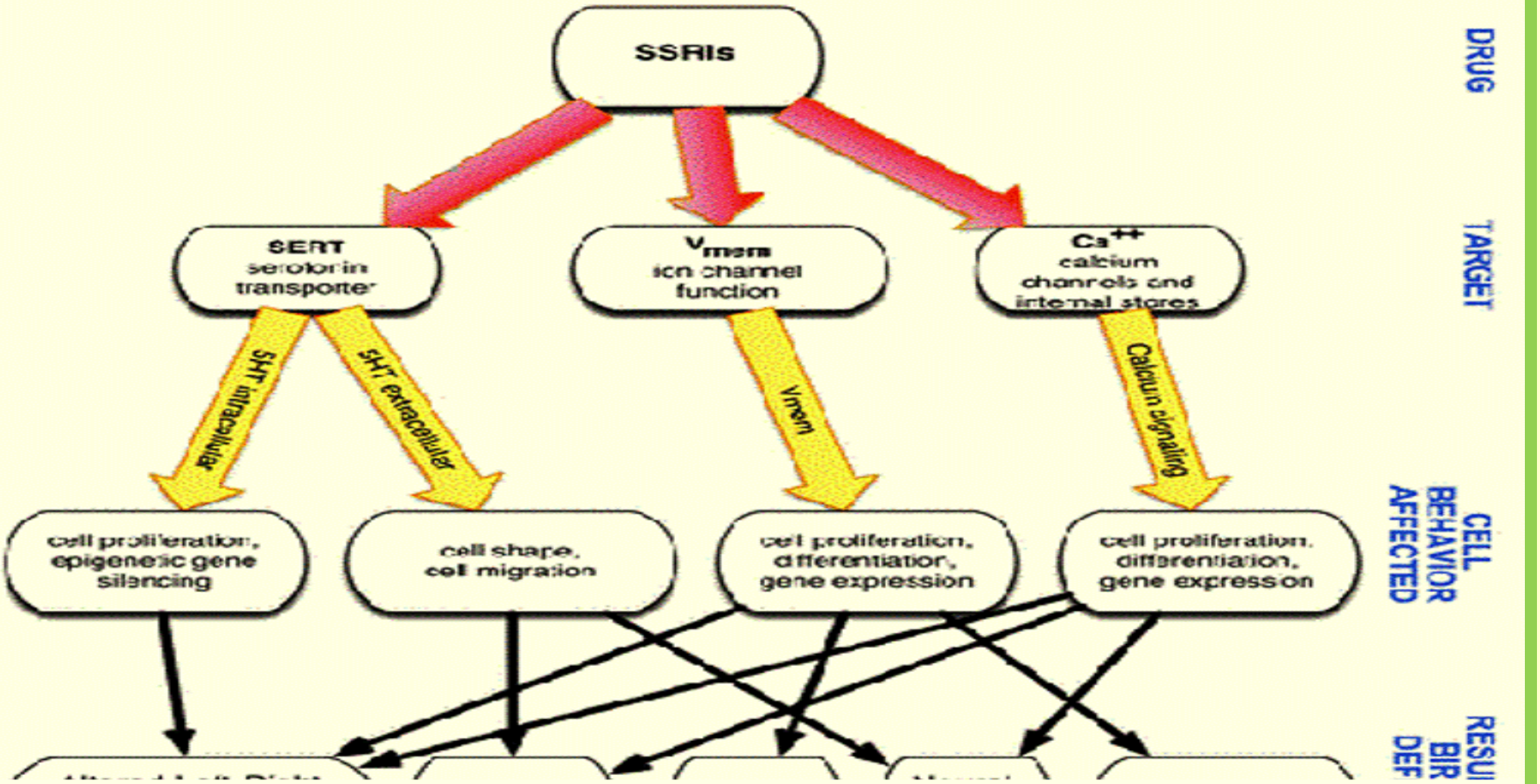
Spontaneous teratogenesis is attributed to disturbed genetic regulation of development that can happen through different pathogenetic mechanisms including: abnormal post-fertilization genomic rearrangements, enhanced transposon activity, abnormal

chromosomal rearrangements and aberrations in early stages of embryonic development, **defective genetic imprinting mechanisms**, **spontaneous mutations** of genes responsible for regulation and synchronization of different stages of development and many others.

B. Induced teratogenesis signifies abnormal development caused by exposure of the mother-embryo-fetus to the deleterious effects of **teratogenic agents** or to the pathological consequences of maternal-related conditions that interfere with normal development.

Spontaneous Teratogenesis	Induced Teratogenesis
1. Mutations of development-regulating genes 2. Transposon over activity 3. Chromosomal rearrangements 4. Defective Activation-Imprinting mechanisms 5. Spontaneous Genomic rearrangements	1. Exposure to Teratogens 2. Maternal diseases 3. Maternal habits 4. Pregnancy-related conditions

Example Of Different Modes Of Actions Of Teratogens
(Selective Serotonin Reuptake Inhibitors)



Teratogens

Teratogens are factors that can adversely affect normal intrauterine development and result in pathogenesis of congenital malformations. Teratogenic factors include two main categories: extrinsic teratogens and intrinsic teratogenic factors.

A. Extrinsic or external teratogens

These comprise a very wide variety of diverse agents. Maternal and/or embryonic-fetal exposure to these teratogens can result in development of structural congenital malformations. This category includes:

1. **Chemical teratogens.**
2. **Physical teratogens.**
3. **Biological teratogens.**

B. Intrinsic teratogenic factors

These factors comprise a wide spectrum of diverse conditions:

1. **Maternal diseases**
2. **Maternal habits**
3. **Pregnancy-related conditions**
4. **Local uterine abnormalities.**

Teratogens and Teratogenic Factors

Extrinsic-External Teratogens	Intrinsic-Internal Teratogenic Factors
A. Chemical Teratogens **1. Chemical compounds**: Innumerable **2. Drugs**: Anti-Epileptic Drugs, Tricyclic Antidepressant Drugs, Retinoic acid & Vitamin A, Antimitotic Drugs, Tetracyclines, Warfarin, Androgens, Estrogens, etc. **3. Heavy metals**: **Lead**: Hemangiomas, Lymphangiomas, Hydroceles, Undescended testes, VACTERL (vertebral, anal, cardiac, tracheoesophageal fistula, renal and limb abnormalities) association. **Mercury**: Atrophy of the cerebellum and the visual cortex. **Lithium**: Heart, CNS, Ear, Ureter defects. Arsenic, Selenium. Aluminum, Cadmium, Chromium, Indium, Nickel, Platinum, Boron, Tellurium, Thallium, Ytterbium, Zinc (In animals)	**A. Maternal Diseases** 1. Diabetes Mellitus 2. Phenylketonuria 3. Myotonic Dystrophy 4. Hyperthyroidism 5. Hypothyroidism 6. Hyperparathyroidism 7. Malnutrition **B. Maternal Habits** 1. Alcohol addiction (Fetal Alcohol Syndrome) 2. Tobaco smoking 3. Cocaine addiction 4. Marijuana addiction, other drug addictions.
B. Physical Teratogens 1. Particulate radiations 2. Hyperthermia 3. Hyperthermia (Sauna Bathing) 4. Magnetic fields	**C. Local Uterine Abnormalities** **Uterine anatomical malformations** Bicornuate uterus, Bifid uterus **Uterine Benign tumors** Leiomyomas
C. Biological Teratogens **1. Teratogenic viruses** Rubella virus, Cytomegalovirus, Herpes simplex virus, Venezuelan Equine Encephalitis virus, Varicella viruses, Human parvovirus B-19, Zika virus. **2. Fetopathic viruses** Influenza virus, Rubeola virus, Western Equine Encephalitis virus, Variola virus, Vaccinia virus, Hepatitis B virus, Echoviruses, Poliovirus Coxsackievirus. **2. Toxoplasma Gondii**: Congenital Toxoplasmosis **3. Treponema Pallidum**: Congenital Syphilis **4. Malaria Falciparum**: Congenital Malaria	**D. Pregnancy-Related States** **1. Oligohydramnios** Fetal limb contractures (Deformations) Pulmonary hypoplasia **2. Anhydramnios** Pulmonary hypoplasia Fetal Akinesia Deformation Sequence **3. Amnionitis & Chorioamnionitis** Disruption sequences **4. Folic acid deficiency & Folic acid antagonists** **5. Assisted Reproductive Technologies** Hypospadias & genitourinary defects, Nasal Tube defects, gastrointestinal anomalies, CHDs, and chromosomal abnormalities.

Structural and Functional Teratogenic Effects of Maternal Diseases

Maternal Disease	Structural-Functional Teratogenic Anomalies
1. Diabetes mellitus	Defects of the heart: transposition of the great vessels, ventricular septal defect (VSD), and dextrocardia. Central nervous system defects: anencephaly, spina bifida, and hydrocephaly. Renal anomalies: renal agenesis and dysplasia. Skeletal defects: radius aplasia, vertebral dysgenesis, sacral agenesis. Situs inversus, caudal regression syndrome, imperforate anus. Pathophysiological disorders: hyperbilirubinemia, hypocalcemia, vascular thromboses (eg, renal vein thrombosis), and respiratory distress syndrome.
2. Phenylketonuria	Intrauterine and postnatal growth retardation, significant developmental delay, microcephaly, cardiovascular defects, dislocated hips.
3. Hyperthyroidism	Goiter, exophthalmos, restlessness, tachycardia, periorbital edema, ravenous appetite, hyperthermia, cardiomegaly, cardiac failure, and hepatosplenomegaly.
4. Hypothyroidism	Mental retardation, spastic diplegia, deafness, and strabismus.
5. Hyperparathyroidism	Bone demineralization and subperiosteal reabsorption in long bones. IUGR, pulmonary artery stenosis, VSD, and muscle hypotonia
6. Myotonic dystrophy	Fetal hypokinesia and generalized weakness, ptosis, clubfoot, difficulty in respiration and feeding, slow postnatal growth, and mild facial dysmorphism including tenting of the upper lip, and anterior cupping of the ear pinnas.

Pathological Mechanisms of Teratogenesis and Congenital Malformations	
Teratogenic Mechanisms	**Examples of Malformations**
Failure/Lack of development	**Renal Agenesis**
Arrested/Incomplete development	**Microcephaly**
Incomplete Migration/Positioning	**Pelvic Kidney – Undescended testes**
Incomplete separation	**Syndactyly**
Incomplete closure	**Neutral tube defects**
Redundant/Excessive development	**Polydactyly**
Aberrant morphogenesis	**Meromelia**
Pathogenetic Mechanisms of Teratogenesis and Congenital Malformations	
Transposon Over Activity	**Isolated/MCA syndromes**
Gene Mutations	**Isolated/MCA syndromes**
Chromosomal Abnormalities	**Multiple Congenital Anomalies syndromes**

Examples Of Teratogenic Effects Of Mutations Of Some Genes Involved In Development

- **Segmentation genes**: Sonic Hedgehog, Desert Hedgehog and Indian Hedgehog

 left-right asymmetry, polarity in the CNS, organogenesis and formation of the skeleton
- **Homeobox genes**: 39 identified, embryo can't survive
- **Homeobox-like domain**: MSX2(craniosynostosis) and EMX2(schizencephaly)
- **Paired-box(PAX) genes**: 9 identified

 PAX3 – Waardenburg syndrome

 PAX2 – renal-coloboma syndrome

 PAX6 – aniridia(WAGR syndrome)

Pathological Patterns of Congenital Malformations

1. Malformation

Primary defective development and morphogenesis of an organ.

2. Deformation

Imposed abnormal shaping of a normally developed or developing organ, parts of organs, or tissues.

3. Disruption

Destruction of shape and design of a normally developed or developing organ, parts of organs, or tissues.

4. Dysplasia

Primary defective morphogenesis or development affecting both growth and differentiation of cells and tissues of an organ or specific tissue.

5. Aplasia

Defective growth and organogenesis of an organ, a limb, a body part or a cell line due to primary failure or secondary arrest of development.

6. Hypoplasia

Hypoplasia or deficient proliferation of cells of a developing organ or tissue is a common primary genetic or secondary induced defect of organogenesis. It can lead to underdevelopment and decreased size of affected tissues or organs, e.g., Cerebellar hypoplasia, Thyroid gland hypoplasia, etc.

7. Anaplasia

Anaplasia signifies a unique state of poor cellular differentiation, loss of morphological characteristics of mature cells and loss of cellular orientation with respect to each other. It also refers to a group of morphological changes and physiological processes in a cell (altered nuclear-cytoplasmic ratio, high proliferation index, nuclear pleomorphism, presence of nucleoli, disturbed chromatin structure, altered cytolpasmic architecture, altered cellular connections and many other changes).

Anaplasia is observed only in cells and tissues of congenital tumors, as well as in post-natal malignancies.

Pathological Patterns of Congenital Malformations

A. Malformation

1. Primary defect(s) of morphogenesis of an organ or a structure due to an intrinsically, mostly genetically-determined, abnormality in formation, growth, or differentiation.

2. Malformations are not specific or pathognomonic. The same morphological defect, or even a similar pattern of abnormalities, may occur as:

a. An isolated anomaly in an otherwise normal individual

b. A feature of a syndrome, a sequence, or an association

c. A feature of a chromosome disorder, a single gene defect, a multifactorial disorder, or secondary to a teratogenic effect.

3. Causative mechanisms include: Lack of development or Hypoplasia of an organ or structure (microtia), Incomplete closure of tubular structures (NTDs), Incomplete fusion (Cleft palate), Incomplete separation (syndactaly).

4. Etiologic Heterogeneity of malformations refers to occurrence of grossly similar phenotypic malformations caused by different etiologic mechanisms. For instance, Cleft Lip and/or Palate can happen as a sporadic isolated idiopathic malformation, but it can also be caused by a wide variety of teratogenic factors including:

Intrauterine teratogen exposure
22q deletion
Primary mandibular hypoplasia
Trisomy 13
Amniotic Bands
Focal dermal hypoplasia
Non-syndromic failure of palate closure
Kniest dysplasia
Gorlin syndrome
Autosomal dominant Van de Woude syndrome
Antenatal Corticosteroids

Pathogenetics of Congenital Malformations

1. Congenital malformations of developing embryos/fetuses may result from a variety of genetic as well as non-genetic factors exerting their teratogenic effects during development.

2. Genetic factors predisposing to development of congenital malformations might be primary inherited genetic defects or acquired genetic defects.

A. Primary inherited genetic defects might be existing from the beginning of fertilization due to participation of parental ova/sperms with structural genic/chromosomal in fertilization with formation of a zygote with this defect, or participation of parental ova/sperms with functional regulatory defects in fertilization with formation of a zygote with defective developmental regulatory mechanisms.

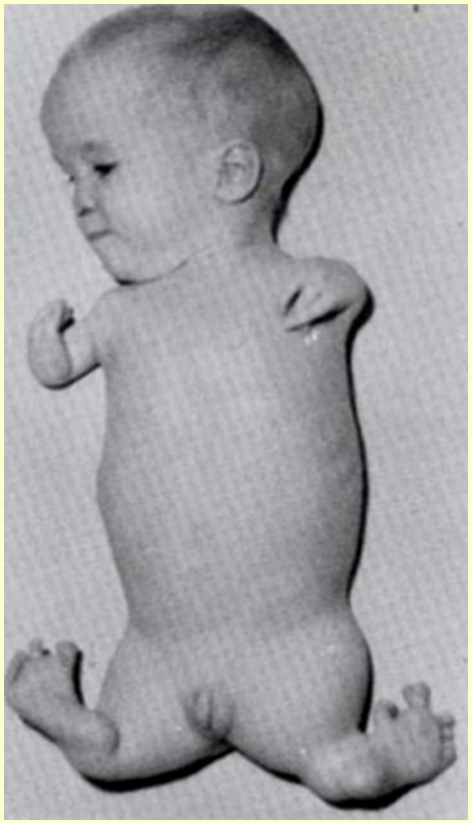
B. Acquired genetic defects result as consequences of either spontaneous mutations or induced mutations occurring during early stages of development. These defects might be selective defects affecting specific regions or parts of the developing embryo/fetus according to the nature and the extent of exposure to the mutagenic factor. Global defects affecting the whole cells of the developing embryo happen when early mutagenic effects involve the whole cellular compartment in the early embryonic stages.

These defects might also be inherited or transmitted to next offspring generaions if they occur early enough during development and affect the genome of developing germinal cells as well.

3. Non-Genetic factors predisposing to development of congenital anomalies comprise external environmental mutagens to which the embryo/fetus might be exposed to during development. These external mutagenic factors include physical mutagens, as particulate radiations, biological mutagens, as teratogenic viruses, and chemical mutagens which comprise an uncountable number of chemical substances in the environment.

The drastic effects of these non-genetic factors predisposing to pathogenesis of congenital malformations span a wide spectrum of defects. Examples include congenital structural malformations, congenital functional derangements, congenital tumors, chromosomal abnormalities, as well as uncountable number of genetic errors with idiopathic phenotypes.












A



B. Deformation

1. Deformations signify abnormalities of shape or position of a part or a region of the body caused by extrinsic non-disruptive mechanical forces on a normally developed or developing structure.

2. Deformations occur due to external constraints exerted on targeted fetal structures. They are caused by factors which restricts the mobility of the fetus, so causing prolonged compression in an abnormal position.

3. Examples of deformations include:

Clubfoot, Congenital hip dislocation, Craniofacial asymmetry, Over folded ears.











C. Disruptions

1. Disruptions are structural defects resulting from destructive damage imposed on normally developed or developing structures leading to death of regions or tissues of affected organs or structures.

2. Disruptions may be caused by mechanical forces, intrauterine infections, or even vascular insults.

3. Examples include: Loss of digit due to amniotic band constriction, lack of normal limb development due to intrauterine vascular accident.





D. Dysplasia

Dysplasia refers to abnormality of morphogenesis or development affecting both growth and differentiation of an organ or tissue.

Dysplasia is a primary malformation defect. It can affect the cells of an organ or system (microscopic dysplasia, e.g., Myelodysplastic syndromes) or affect the shape of the organ (macroscopic dysplasia, e.g., skeletal dysplasias).





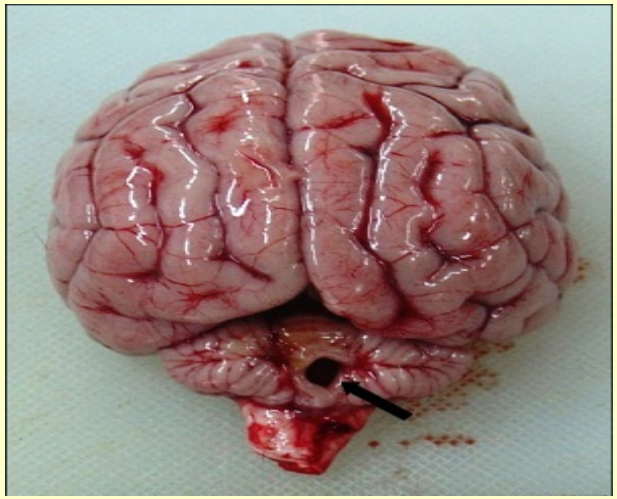
E. Aplasia/Agenesis

Renal aplasia, Thymic gland aplasia, Pure red cell aplasia, Local skin aplasia (Aplasia Cutis Congenita, etc).

F. Hypoplasia

Enamel hypoplasia, Cerebellar hypoplasia, Renal hypoplasia.







G. Anaplasia

Clinical Presentations of Congenital Malformations

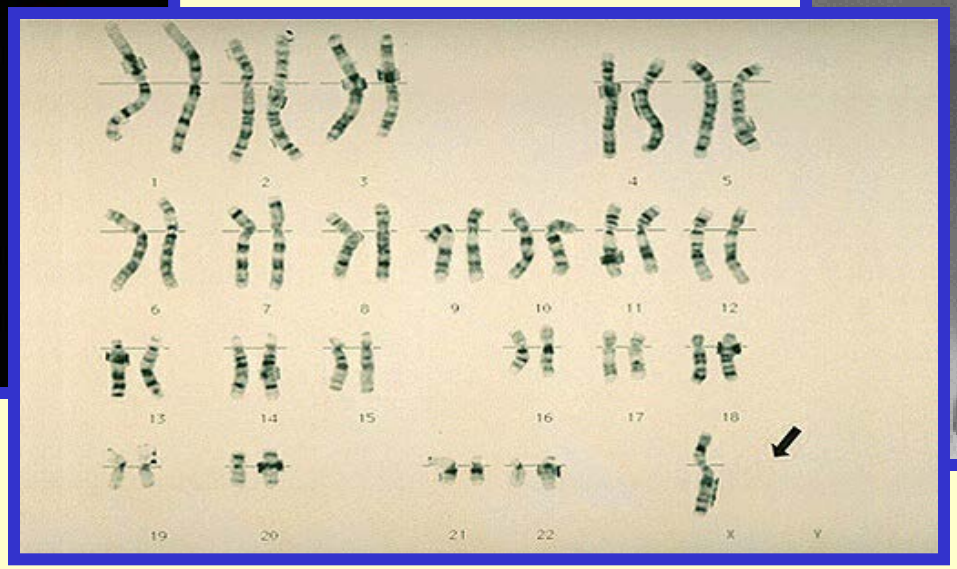
Presentation	Description
Sporadic	**Single occurrence**
Familial	**Positive family history of same anomaly**
Isolated	**Only anomaly detected in person/patient**
Sequence	**Constellation of defects due to a cascade of effects related to a single known, or presumed, localized abnormality (malformation, deformation, disruption).** **Example: Potter sequence: Renal dysplasia ⇨ oligoamnios ⇨ pulmonary hypoplasia & facial dysmorphism.**
Syndrome	**Group of multiple anomalies that can be traced to a common etiologic origin.** **Genetically-determined conditions due to single gene disorder, multiple genes or** **Chromosomal abnormalities (Down syndrome, Marfan syndrome).**
Association	**Non-random occurrence of a combination of several anomalies, not yet identified as a specific sequence or syndrome, that occur more often together than by chance alone. Examples: (VATER, VACTERL, CHARGE associations)**

Turner syndrome









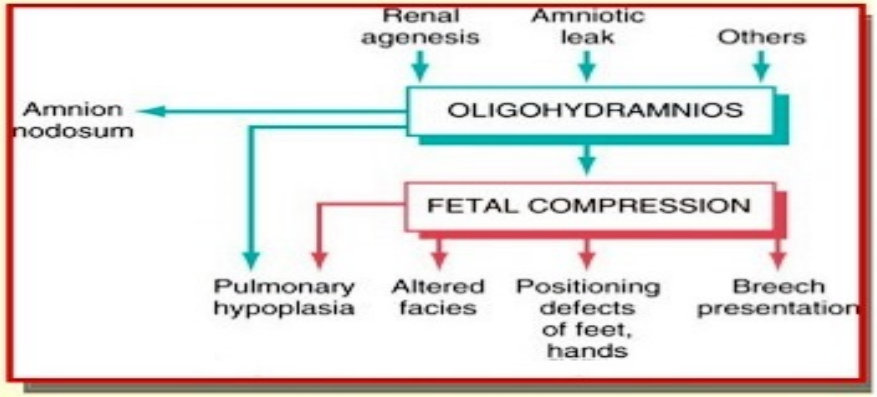
VATER(VACTERL) Association

- Vertebral Anomalies
- Anal
- Cardiac defects
- Tracheo-esophageal Fistula
- Renal/Radial anomalies
- Limb defects
- No specific genetic pattern or inheritance
- Incidence 16/100,000

CHARGE Association

- Coloboma
- Heart disease
- Atresia of choanae
- Retarded growth
- Genital anomalies
- Ear anomalies

Potter sequence





Prophylactic Teratology

Prophylaxis and prevention of congenital malformations can be achieved for some specific anomalies with known etiology.

1. **Vaccination of girls and future mothers against rubella infection.**
2. **Adequate nutritional intake of folic acid / iodine.**
3. **Avoidance of smoking, alcohol, addiction drugs (speed,Tina, crank, ice, etc).**
4. **Avoidance of intake of drugs with known or suspected teratogenic potential, unless no other options exist.**
5. **Absolute avoidance of CT investigations during pregnancy.**
6. **Adequate antenatal care to avoid pregnancy-related complications.**
7. **Proper medical care of maternal diseases, particularly Diabetes Mellitus, before and all through gestation.**
8. **Antenatal fetal care, fetal therapy, and fetoscopic surgical procedures can help in early detection and treatment of many fetal anomalies including: CAH, myelomeningocele, diaphragmatic hernia, twin-twin transfusion, congenital cystic malformations of the lung, sacrococcygeal teratomas, ureteric obstruction, etc.**

www.archive.org/details/MedicalGenetics